Tamoxifen versus aromatase inhibitors as adjuvant therapy in premenopausal women with hormone receptor-positive breast cancer; effects on sexuality and the female reproductive system

A thesis submitted in fulfilment
of the requirements for the degree of
Master of Science in Medical Research Methodology

By

Aглаия Skolariki

Thessaloniki, May 2019
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Abbreviations

AI - Aromatase Inhibitor

AIMSS – Aromatase-Inhibitor-associated Musculoskeletal Syndrome

ANOVA – Analysis of Variance

BCS - Breast-conserving Surgery

BR - Breast Reconstruction

CI – Confidence Interval

CNS - Central Nervous System

DFS - Disease-free Survival

DK - “I don’t know”

EORTC - European Organization for Research and Treatment of Cancer

ER - Estrogen Receptor

ER+ - Estrogen-Receptor Positive

ET - Endocrine Therapy

FSFI - Female Sexual Function Index

GDPR - General Data Protection Regulation

GnRH - Gonadotropin-Releasing Hormone

HER2 – Human Epidermal Growth Factor Receptor 2

HPV – Human Papilloma Virus

IDK - I don’t know

IQR – Interquartile Range
LHRH - Luteinizing Hormone-Releasing Hormone
LND - Lymph Node Dissection
LSE - Lower Secondary Education
MD – Missing Data
NA – Not Available
OFS - Ovarian Function Suppression
OR – Odds Ratio
PE - Primary Education
PFDI-20 - Pelvic Floor Disability Index
PFIQ-7 - Pelvic Floor Impact Questionnaire
QLQ-BR23 - Quality of Life Questionnaire - Breast Cancer Module
QoL – Quality of Life
Q1 – Quartile 1
Q3 – Quartile 3
SD - Standard Deviation
SERM - Selective Estrogen Receptor Modulator
STD – Sexually Transmitted Disease
UDI-6 - Urogenital Distress Inventory
UGT - Urogenital Tract
USE - Upper Secondary Education
VAI – Vaginal Atrophy Index
VET - Vocational Education and Training
Abstract

Objectives: The objective of this cross-sectional study was to compare the prevalence of sexual dysfunction in premenopausal women with breast cancer in Greece, who receive adjuvant endocrine therapy with either tamoxifen or aromatase inhibitors (AI), with or without ovarian function suppression (OFS). A second endpoint was to investigate and compare the incidence of genitourinary symptoms and conditions.

Methods: A questionnaire was distributed on hardcopy and through an online platform, to Greek-speaking women of 18 years of age or older, who had been receiving adjuvant endocrine therapy for breast cancer for at least three months and were deemed premenopausal/perimenopausal at diagnosis. The questionnaire included investigator-generated items regarding demographics, sexual and gynecologic history, as well as validated instruments for sexual functioning and urogenital tract disorders (FSFI, QLQ-BR23, UDI-6 and PFIQ-7).

Results: Of the 108 received responses, 70 were considered eligible for analysis. Most participants were currently on treatment with tamoxifen/OFS (N=35). Women on AI/OFS reported great deterioration of their sex life compared to women on tamoxifen with OFS (p=0.001). Sexual dysfunction was evident in 74% (N=49) of our participants, as defined by the cutoff value of 26 for the FSFI total score (median: 17.45, IQR=26.18). In particular, women on AI/OFS had significantly lower scores compared to those on tamoxifen with (20.8, 95%CI [14.58;22.67] vs 8.8, 95%CI [4.86;13.60], p=0.040) and without OFS (19.95, 95%CI [13;22.91] vs 8.8, 95%CI [4.86;13.60], p=0.039). Sexual enjoyment of women on AI/OFS was significantly affected compared to women on tamoxifen with or without OFS (p=0.019 and p=0.020, respectively). No differences in vaginal atrophy symptoms or gynecologic conditions were detected.

Conclusions: Sexual dysfunction is highly prevalent in premenopausal women on endocrine therapy, especially in those treated with aromatase inhibitors and ovarian function.
suppression. Health professionals should promote discussions with their patients in order to decide the optimal treatment choice.
Introduction

Breast cancer is one of the most common malignancies and a leading cause of cancer death for women worldwide. A female's lifetime risk of developing invasive breast cancer is estimated at around 12%, but the individual risk varies depending on age, ethnicity, lifestyle, family and reproductive history. According to recent data, over 60,000 new cases of breast cancer are expected to be diagnosed in 2019. (1,2) Nonetheless, advancements in terms of preventive measures, early diagnosis and effective treatment have drastically transformed the course and impact of the disease on patients and their families, thus constituting one of Oncology's greatest success stories, so far.

In particular, incidence rates for breast cancer have demonstrated a steady decline from 1999 to 2007, with mortality trends decreasing since the mid-1970s. (3) Despite the fact, that a 40% decrease has been noted in death rates during the period 1989-2016, the numbers regarding breast cancer incidence in women have been on the rise, an observation mostly attributed to lifestyle factors, prevalence of obesity and parity decline. Still, breast cancer survival, for all stages considered, remains as high as 90%. (1,4)

These encouraging results regarding survival, especially in patients with early-stage disease, have raised issues concerning the quality of life of women burdened by this diagnosis, who may have been through surgical treatment, radiation and systemic therapy, each one of them associated with a different spectrum of side effects. From the moment of diagnosis, female patients have to deal with a life-threatening disease and endure a series of treatment-associated body changes, that can cause serious psychological distress, distorted body image, low self-esteem and sense of femininity, often leading to sexual dysfunction. (5–8) From breast loss or disfigurement, chemotherapy-induced alopecia and lymphedema to weight gain and menopause-related symptoms, patients and their physicians are expected to cooperate in handling each challenge as it arises, weighing the consequences and reaching a joint decision. (9–11)
These decisions are becoming much more challenging in premenopausal patients with early-stage breast cancer, when fertility and reproductive issues are intertwined and the management plan needs to be adaptable and individualized. Premenopausal women should be offered oncofertility counseling and detailed information on fertility preservation solutions before receiving treatments that would affect and possibly damage their reproductive function, taking into account patient’s age, risk of recurrence, marital status and family planning. (12,13)

A multidisciplinary approach is required especially for those aged ≤40 years at breast cancer diagnosis. This specific cluster of patients has been associated with more aggressive tumor phenotypes, of higher grade and size, often attributed to a relative delay in diagnosis. Despite adjuvant therapy, these factors ultimately lead to a poorer prognosis, with higher lifetime recurrence rates. (14–18) On top of that, the impact on the everyday lives, personal relationships and work routine of these patients is tremendous, as they struggle through psychological sequelae of cancer diagnosis and menopause transition caused by their treatment. This abrupt change in menopause status combined with appearance and body image concerns, negatively affects their libido and sexual health, often leading to poor quality of life. (19,20)

Current treatment approaches in premenopausal women with early-stage breast cancer depend largely on the breast cancer type and individual risk of relapse. The estrogen-receptor positive (ER+) phenotype represents approximately 60% of the cases in premenopausal patients, although it is much more common in postmenopausal women. (21–23) Patients with hormone sensitive breast cancer are candidates for adjuvant endocrine therapy (ET) that offers substantially improved survival prospects, with many trials suggesting the extension of its duration from five to ten years, depending on patient’s risk of recurrence and treatment-associated risk of toxicities. (24–27) Treatment options include agents like tamoxifen, which is a selective estrogen receptor modulator (SERM), and aromatase inhibitors (AIs), with or without the integration of ovarian ablation methods. (28–30)
Tamoxifen acts as a competitive antagonist of the estrogen receptor (ER), therefore inhibiting the effect of estrogens on the mammary tissue. (31) However, being a selective modulator, it can produce estrogen-like changes on other tissues, depending on the ambient estrogen levels and menopausal status. Its stimulatory effect on the ERs, which regulate multiple biological activities such as metabolism, cardiac and bone remodeling, growth and development of reproductive organs, is responsible for the diverse adverse events associated with its use. (32) Apart from increasing the incidence of thromboembolic disease, its proliferative activity in the endometrium has been associated with a noteworthy risk of endometrial hyperplasia and carcinoma, as well as a modest increase in the uterine sarcoma rates. (33,34) These agonist effects are mostly observed in postmenopausal women, as their endogenous estrogen levels are considerably low, whereas in premenopausal patients the estrogen antagonist effect is predominant. This antiestrogenic activity in the hypothalamic thermoregulatory center of the central nervous system (CNS) is considered the primary cause for the manifestation of vasomotor symptoms, which premenopausal women experience to a greater degree than older patients. (35–37) Several other abnormalities have been documented regarding the female reproductive organs, with cervical, endometrial polyps and ovarian cysts constituting a common finding. On the vaginal tissue, the effects are complex, but women often mention vaginal dryness and dyspareunia. Even less clear is the impact of long-term use on the ovaries, as tamoxifen is considered a potent inductor of ovarian function. (38–41)

Aromatase inhibitors are a different category of ET used in the adjuvant setting of early breast cancer. Three agents (exemestane, letrozole, anastrozole) are currently approved, with no proven superiority of one over the other. (42,43) While AIs are the standard approach in females after menopause, they are only recommended to premenopausal women with high-risk for relapse features and the treatment is always accompanied by ovarian function suppression (OFS). (44,45) AIs act on the enzyme aromatase, which peripherally converts androgens to estrogens, by blocking or inactivating it, hence lowering the circulating estrogen levels. In premenopausal women, this reduction in plasma estrogen levels can induce, through a feedback mechanism in the hypothalamic-pituitary-gonadal axis, excessive and undesired
production of estrogens from the functioning ovaries. (46,47) This can be overcome by suppressing ovarian function, either permanently with surgical procedures or irradiation, or temporarily with pharmacologic interventions.

Premenopausal women who undergo adjuvant ET with AIs and OFS experience the adverse effects of premature menopause, which range from hot flashes and vaginal atrophy, to osteoporosis and increased cardiovascular risk. (48–51) Arthralgias, joint stiffness and bone pain are a common side-effect of AIs and are referred to as AI-associated musculoskeletal syndrome (AIMSS). (49,52) Furthermore, vaginal and urogenital atrophy due to peripheral blockade of estrogen production, that manifest with urinary incontinence, recurrent infections, dyspareunia and vaginal symptoms, can influence tremendously the sex life and daily activities of a previously healthy female of reproductive age and have been considered more prominent in women on AIs than those on tamoxifen. (48,53,54) On top of that, ovarian ablation or ovarian function suppression, through oophorectomy, radiotherapy or pharmacological agents such as gonadotropin-releasing hormone (GnRH) or luteinizing hormone-releasing hormone (LHRH) agonists, has been associated with an additional risk for the manifestation of sexual dysfunction. (55,56) Ultimately, these complications along with fertility concerns can severely damage the patient’s quality of life.

Recent recommendations regarding the duration and choice of the adjuvant ET, point towards the extension of treatment from five to ten years and the addition of OFS to either tamoxifen or AI. (57,58) The publication of the updated results of two large, randomized trials (SOFT and TEXT) revealed benefit for a median 8-year follow-up in disease-free survival (DFS) of both tamoxifen and exemestane combined with OFS over tamoxifen alone. Overall survival was also improved for tamoxifen plus OFS compared to the single agent (93.3 versus 91.5 percent; HR 0.67, 95% CI 0.48-0.92). Distant recurrence-free survival did not appear to change significantly with the addition of OFS, except for the exemestane arm of the trial. On the other hand, toxicities and grade 3 adverse reactions were significantly more frequent in females who received OFS, with side-effects from the musculoskeletal and reproductive system, as well as sexual dysfunction, being predominant. (55)
Currently, clinical practice guidelines suggest that premenopausal women in high risk for recurrence, which is attributed based on their anatomic stage, pathologic features and established prognostic factors, would benefit from ET plus OFS for a total of ten years, with AIs offering possibly improved outcomes. (45,47,56,57) The use of OFS is thus broadened to women with stage II and III breast cancer and to those with earlier stages, to whom chemotherapy might be considered. Since these criteria for risk of relapse are still in process and not concrete enough, there are still grey zones regarding these group of patients and the decision needs to be individualized based on recurrence risk reduction and treatment-related complications. (59,60) All patients need to be fully aware of the complete spectrum of toxicities associated with each type of ET and participate actively in decision-making along with their treating physician and primary care providers, in order to comply with a long-lasting treatment plan.

**Aim of this study**

In the light of recent evidence, the numerous challenges that clinicians face during treatment of women of reproductive age, as well as the ongoing debate over their optimal management, we aim to investigate and compare the impact of three different options of ET (tamoxifen, tamoxifen plus OFS, aromatase inhibitors plus OFS) on the reproductive system and sexual function of premenopausal women with early-stage breast cancer. This frequently underestimated parameter, if not managed appropriately, can become the source of gradual degradation of quality of life, leading to reduced tolerability, poor treatment adherence and consequentially to inferior treatment outcomes. Hence, our study will attempt to shed light on the effects of ET on gynecologic and sexual health of this subgroup of breast cancer patients, raising awareness and providing clinicians and their patients with insight and knowledge on these issues, so that a personalized approach with timely diagnosis and effective counseling is incorporated in clinical practice.
Materials and Methods

Study design and setting

We performed a cross-sectional study of Greek-speaking, premenopausal women with early-stage breast cancer, who had been on adjuvant ET for at least three months and were older than 18 years. The duration of the study accrual was five months, from November 2018 to March 2019. All females were either patients on follow-up care at the “Theagenio” Cancer Hospital of Thessaloniki, a tertiary specialized cancer center in Northern Greece, or were invited to participate through an open invitation by the Hellenic Association of Women with Breast Cancer “Alma Zois”, a non-profit organization for breast cancer survivors in Greece. Approval for the conduct of the study was obtained in each case by the institutional review board. Participants were invited to complete the survey anonymously and were handed a hardcopy of our questionnaire, labeled “Tamoxifen versus aromatase inhibitors as adjuvant therapy in premenopausal women with hormone receptor-positive breast cancer: effects on sexuality and the female reproductive system”, accompanied by the document for their written consent, in an opaque envelope. Consequently, they were instructed to send it through postal service, without any indication of the sender’s details. Alternatively, patients were able to complete the online version of our questionnaire through an online survey tool (SurveyMonkey Ink., Location: San Mateo, California, USA, main website: www.surveymonkey.com). The link to our web survey was sent through email to those who requested it and implied consent was described in the questionnaire’s cover letter. No personal data could be traced to the survey respondent and information gathering was compliant with GDPR guidelines.

Eligibility criteria

All participants were on adjuvant therapy with either tamoxifen or AI with or without pharmaceutical addition of ovarian function suppression. Eligibility criteria referred to age, pre- and perimenopausal status, treatment duration and switch to other agents of ET (Table 1).
Inclusion Criteria | Exclusion Criteria
--- | ---
Women over 18 years of age | Switch to a different agent of endocrine therapy
Early breast cancer after definitive local treatment | Treatment duration less than three months
Pre/perimenopausal at diagnosis | Menopause, independent of cause
Adjuvant treatment with tamoxifen/AI +/- OFS | 
Fluency in Greek | 

*Table 1 Eligibility criteria*

Eligible patients, who continued post-treatment surveillance at “Theagenio” Cancer Hospital, were recognized based on their chart reviews and contacted at their follow-up visits. The rest of the participants were screened based on their answers on the survey, which would reveal any excluding criteria. Age, treatment duration and previous ET with a different agent, were determined through baseline questions of the survey. Assessment of the participants’ premenopausal and perimenopausal status was based on factors such as age, with special caution given to women over 40 years of age, presence of normal menstruation at diagnosis, menstrual cycle irregularities and the type of the administered ET. Therefore, women who received OFS as part of their treatment were included. Instead, patients who were set menopausal, independent of cause, at diagnosis (i.e. due to previous oophorectomy) were excluded from the study. Likewise, women whose menopausal status could not be extrapolated from the abovementioned parameters, with questionable eligibility to our study since all information were self-report and no hormonal testing was required, were not included.

**Ethics Approval**

This study was approved by the Institutional Review Board of Theagenio Cancer Hospital (Protocol number 20622/31.10.2018) and the Department of Medicine of Aristotle University of Thessaloniki (Protocol number 268/30.10.2018).
Questionnaire

The survey consisted of demographic questions, investigator-generated items regarding medical conditions, with emphasis on menstrual, obstetric and gynecologic history, breast cancer-specific information as well as four separate instruments assessing the quality of life (EORTC QLQ-BR23), sexual functioning (FSFI), urogenital and pelvic floor disorders (UDI-6, PFIQ-7) (Appendix). (61–63) Investigator-generated questions assessing sexual and gynecologic health had response options based on a Likert-type scale, as well as stand-alone questions assessing additional symptoms. Questions about the frequency of symptoms could be answered with a 5-point scale, each one represented by a numerical value, so that the higher the score, the greater the frequency of the symptom in question (1- “very rarely or never” to 5- “very frequently”). In closed-ended questions we used yes/no answers (1- No, 5- Yes). Two further response categories of “I don’t know” (DK) and “I didn’t attempt intercourse” were added, according to the question’s context. The relative frequencies of the responses to the aforementioned categories were measured; Unavailable data (DK responses) regarding the variable of interest were not included in the analysis, therefore handled as missing values. Responses of no sexual intercourse would be assigned a zero value. Items were combined based on the system or condition described. Relative frequencies were used to describe categorical data, and an overall score would be obtained according to the frequency of symptoms associated with vaginal atrophy (Table 2, Appendix).

The Vaginal Atrophy Index (VAI) was defined as the average score calculated by 8 items investigating manifestation of vaginal bleeding, vaginal discharge, frequency of dyspareunia and urogenital tract infections, vaginal dryness, pruritus and redness. Likert-type items had a score range 1 to 5 and yes/no questions were scored 5/1, respectively. Unavailable items (such as DK responses) and missing values were not included in the average score, while responses of no sexual intercourse were marked as zero. Consequently, the overall index score range was 0.75 to 5 (including women who did not attempt intercourse), with three levels of frequency:

- 0.75 – 2.08 “rare condition”
• 2.09 – 3.42 “frequent condition”
• 3.43 – 5 “very frequent condition”

To ensure content validity, a multidisciplinary expert panel was gathered during the development of the questionnaire, formed by urogynecologists, medical oncologists and a clinical psychologist. Content/face validity was further indicated by the exceptionally low rate of missing values. For internal consistency we implemented Cronbach’s alpha.

<table>
<thead>
<tr>
<th>Item number</th>
<th>Symptoms/Conditions</th>
<th>Type of question</th>
<th>Descriptive statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>35,36</td>
<td>Manifestation of gynecologic conditions before and after treatment</td>
<td>Multiple choice</td>
<td>Relative frequencies</td>
</tr>
<tr>
<td>39,40,41</td>
<td>Endometrial hyperplasia/endometrial cancer</td>
<td>Closed-ended (yes/no/DK)</td>
<td>Relative frequencies DK responses-excluded</td>
</tr>
<tr>
<td>42</td>
<td>Other gynecologic cancer</td>
<td>Closed-ended (yes/no/DK)</td>
<td>Relative frequencies DK responses-excluded</td>
</tr>
</tbody>
</table>
| 43,44,45,46,47,48,49,50 | Vaginal atrophy (including vaginal bleeding, dyspareunia, vaginal discharge etc.) | • 5-point Likert scale (score range: 1 to 5*)  
• Closed-ended (yes/no/DK) | Multi-question index  
– Average score (range 0.75 – 5)  
DK responses-excluded |

Table 2 Gynecologic health assessment – Questionnaire items and scoring characteristics, DK: “I don’t know”, * 43-44 item: score range 0 to 5
EORTC Quality of Life Questionnaire – Breast Cancer Module (QLQ-BR23)

The EORTC QLQ-BR23 has been the instrument of choice for breast cancer patient assessment of quality of life since 1996. (64) It comprises of 23 questions, with functional and symptoms scales that assess body image, future perspective, sexual functioning and enjoyment, breast and arm symptoms, as well as complications associated with systemic therapy and treatment-induced alopecia. We incorporated it in our survey as a first indicator of sexual functioning, based on the relative domains. Furthermore, we investigated the association between sexual dysfunction in premenopausal women on different types of ET and other measures of quality of life (i.e. body image, future perspective etc.), that could possibly act as effect modifiers for our outcome. Scoring was consistent with EORTC guidelines and missing values from multi-item scales would be imputed, considered that at least half the items were completed. (65) Scores for missing data from single-item measures would be set to missing, instead. A linear transformation to a scale of 0 to 100 was applied to all scores. For functional scales (body image, sexual functioning and enjoyment, future perspective), a high score would be interpreted as a high or healthy level of functioning, whereas for symptom scales or items (systemic therapy side effects, breast and arm symptoms, upset by hair loss), the higher the score the greater the severity of the associated symptom or problem (Table 3). The QLQ-BR23 has been validated as a reliable instrument for assessment of quality of life in breast cancer patients in Greece. (66)

<table>
<thead>
<tr>
<th>Item Numbers</th>
<th>Item Range</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Functional Scales</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body image</td>
<td>9-12</td>
<td>3</td>
</tr>
<tr>
<td>Sexual functioning</td>
<td>14,15</td>
<td>3</td>
</tr>
<tr>
<td>Sexual enjoyment</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>Future perspective</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td><strong>Symptom scales/items</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic therapy side effects</td>
<td>1-4,6,7,8</td>
<td>3</td>
</tr>
</tbody>
</table>
Female Sexual Function Index (FSFI)

The FSFI is a 19-item instrument, developed to measure sexual functioning during the past 4 weeks, in females. (61) The questions investigate six fundamental domains, which include desire, arousal, lubrication, orgasm, satisfaction and pain and an overall score is consequently obtained based on the individual scores of each domain. The overall score ranges from 2 to 36, with a cutoff value at 26.55, considered by Wiegel et al. as optimal to discriminate women with and without sexual dysfunction (Table 4). (67) However, according to the study of Zachariou et al. for the translation and validation of the Greek version of FSFI, a score under 26 was considered most suitable to define subjective sexual dysfunction in Greek females. (68)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Questions</th>
<th>Score Range</th>
<th>Factor</th>
<th>Minimum Score</th>
<th>Maximum Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desire</td>
<td>1, 2</td>
<td>1 – 5</td>
<td>0.6</td>
<td>1.2</td>
<td>6.0</td>
</tr>
<tr>
<td>Arousal</td>
<td>3, 4, 5, 6</td>
<td>0 – 5</td>
<td>0.3</td>
<td>0</td>
<td>6.0</td>
</tr>
<tr>
<td>Lubrication</td>
<td>7, 8, 9, 10</td>
<td>0 – 5</td>
<td>0.3</td>
<td>0</td>
<td>6.0</td>
</tr>
<tr>
<td>Orgasm</td>
<td>11, 12, 13</td>
<td>0 – 5</td>
<td>0.4</td>
<td>0</td>
<td>6.0</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>14, 15, 16</td>
<td>0 (or 1) – 5</td>
<td>0.4</td>
<td>0.8</td>
<td>6.0</td>
</tr>
<tr>
<td>Pain</td>
<td>17, 18, 19</td>
<td>0 – 5</td>
<td>0.4</td>
<td>0</td>
<td>6.0</td>
</tr>
</tbody>
</table>

| Full Scale Score Range | 2.0 | 36.0 |

*Table 4 FSFI Scoring System*
Although FSFI has been deployed in numerous studies measuring sexual functioning in both sexually active and inactive women with satisfactory reliability and acceptability, its applicability to women who are currently unpartnered, as the questions are mainly focused on partnered sexual intercourse, is questionable. (69–71) To overcome this issue, we added the option of “no sexual partner” in questions 14 and 15. (69) The overall score for respondents who selected the aforementioned option would be obtained without taking into account these two questions and the satisfaction domain would be therefore multiplied by a factor of 1.2. Respondents whose FSFI questionnaire was incompletely filled in, were not included in the sexual dysfunction analysis.

**Urogenital Distress Inventory (UDI-6) and Pelvic Floor Impact Questionnaire (PFIQ-7)**

UDI-6 is a validated, short form questionnaire, composed of 6 items and a subscale of Pelvic Floor Disability Index (PFDI-20) that evaluates urinary incontinence in a response scale from 0 to 4 (0- “not present”, 1- “not at all” to 4- “quite a bit”). PFIQ-7 is another self-report instrument that measures the degree that problems and symptoms related to three different systems (Bladder/Urine, Bowel/Rectum, Vagina/Pelvis) have affected daily activities, relationships, functional and emotional status over the past 3 months, in a 4-point scale (0- “not at all” to 3- “quite a bit”). (63) For our survey, solely the subscales regarding the bladder/urine and vagina/pelvis symptoms were administered. Both questionnaires have been translated in Greek and validated in a Greek female population with pelvic floor disorders. (72) The mean value for all answered items within the corresponding scale was calculated and then multiplied by a factor to obtain the scale score which ranges from 0 to 100, with higher scores indicating higher distress. Missing items were substituted by the mean score of the rest answered items. (73)

**Missing Data**

Study results were obtained and based solely on the survey’s responses. Respondents that did not specify the type of ET, as well as those that did not proceed to respond to questions besides demographics, were not included in the analyses. Unavailable data regarding age and
chemotherapy administration that were necessary for sample stratification, were an additional exclusion criterion. Missing data (MD) in demographic questions were insignificant (~0.3%) and therefore, ignored. Likewise, the method of complete-case analysis was implemented in FSFI items’ responses and in responses about gynecologic conditions, as the rate of missing values was quite low (~5.7% and 0.3%, respectively). Further missing data were handled using the method of imputation.

**Statistical Analysis**

A database was created through data extraction from the SurveyMonkey platform, where all responses, including those on hardcopy, were registered. The primary objective of the study was to determine whether differences in sexual activity occur among premenopausal women on tamoxifen compared to women on AIs plus OFS or tamoxifen plus OFS. An overall FSFI score and the sexual functioning and enjoyment subscale scores of the QLQ-BR23 were used as methods of measurement. Secondary outcomes, including gynecologic disorders, vaginal and urogenital atrophy symptoms, were measured by the UDI-6, PFIQ-7 subscales and symptom scales assessing gynecologic health. Our original protocol described stratified samples according to age (≤40 and >40 years) and receipt of chemotherapy and further subgroup analyses according to disease stage, occupational and marital status. In order to detect a difference in sexual functioning among women of the three groups, with a rather small Cohen’s d effect size of 0.2, 80% power and level of significance at 0.05, approximately 80 study participants would be required to form each group. (74,75) To allow an attrition rate of 25%, stratified sampling, subgroup analyses and control for confounding factors, the sample size should increase substantially. (75–80) A larger effect size of 0.5 would require groups of 14 people. To explore the feasibility of our research project, we decided to run a pilot study. A total of approximately 130 questionnaires were distributed in a 5-month period, opting to attain a sample size of 75 participants. An exploratory analysis would follow to describe our sample and the variables of interest. Quantitative data were expressed as means or medians with standard deviations (SD) or interquartile ranges (IQR), respectively. The analysis of variance (ANOVA) or the Kruskal-Wallis test were implemented for multiple group comparisons. Categorical variables were
expressed as frequencies with percentages and compared using chi-square or Fisher’s exact test. Statistical analyses were performed using R Statistical Software (RStudio Version 1.1.456). Regression analyses were performed to investigate the association of the independent variables of age, chemotherapy administration, marital and occupational status, type and duration of ET with the occurrence of sexual dysfunction. All p values presented are two-tailed, with p values lower than 0.05 considered statistically significant. To correct for the familywise type error I rate, we applied the Bonferroni correction and p-values were adjusted.

Results

Study Flowchart

A total of 130 questionnaires were distributed and/or sent online, of which 107 responses were received. Four of them were completely blank and two of them were partially answered (only demographics were filled in), therefore excluded from the analysis. Three of them did not include their date of birth, nine of them did not specify the agent of ET or whether they received OFS and two of them had switched from another agent to their current treatment, thus, were also excluded. Another 15 respondents were not included as their treatment duration (less than 3 months) and their menopausal status (oophorectomy) did not match the eligibility criteria. Two more women that received AIs without OFS were not analyzed, as their premenopausal status was questioned. Overall, 70 responses were analyzed: 19 women (27%) received tamoxifen only, 37 (53%) of them were in the tamoxifen plus OFS group and the rest 14 women (20%) were under treatment with AIs plus OFS (Figure 1).
Figure 1 Study Flowchart

Sent out questionnaires N=130

Received responses N=107

Unspecified age/ET/PFS N=12 excluded

Unknown premenopausal status N=2 excluded

Incomplete questionnaires N=6 excluded

Duration <3 months Menopausal status ET switch N=17 excluded

Analyzed responses N=70

Tamoxifen + OFS N=37

Tamoxifen N=19

AI + OFS N=14
Participants’ characteristics

Baseline features of the participants assigned to the three groups of ET were compared. All baseline data are presented in Table 5. In summary, the majority of women were married (64%, N=45) with children (72.9%, N=51) and educated beyond secondary level of education (68.6%, N=48). Interestingly, more than one third of them were at that point unemployed (35.7%, N=25). The stage of cancer at diagnosis was mostly unknown to our respondents, but a tendency towards more advanced stages (2A-3A) was noticed and confirmed by the high numbers of women that had undergone axillary lymph node dissection (62.9%, N=44). In addition, only a small proportion of them (11.4%, N=8) had proceeded to breast reconstruction. More than 80% (N=57) had received radiotherapy and approximately 16% answered positively about their HER2 status (N=11). OFS was administered to most of our participants (72.9%, N=51) combined with tamoxifen as the ET agent of choice for premenopausal women (52.9%, N=37), while an AI was administered to the rest 20% (N=14). Women on tamoxifen monotherapy comprised the third group (27.1%, N=19).

Study groups were formed and an association was detected between HER2 status and the type of ET (p=0.004). Pairwise comparisons that followed, using Fisher’s exact test and Bonferroni correction, revealed that women who were treated with an AI plus OFS had approximately 16 times the odds of those on tamoxifen alone to be HER2 positive (OR: 16.10, 95%CI 1.51-867.09, p=0.021) and 7.5 times the odds of those on tamoxifen plus OFS (OR: 7.54, 95%CI 1.34-49.30, p=0.028). On the other hand, women on monotherapy with tamoxifen had 55% lower odds of being HER2 positive than those who were administered OFS along with tamoxifen but this association was not deemed significant (OR:0.45, 95%CI 0.01-5.02, p=1).

Likewise, administration of chemotherapy or radiotherapy were found to be associated with the type of ET (p=0.030 and p=0.011, respectively). The odds of women on tamoxifen alone to have been administered chemotherapy, compared to those on tamoxifen with additional OFS, were lower by 78%, but this was an insignificant association (OR: 0.22, 95%CI 0.05-0.89, p=0.071). The odds of women on AIs/OFS compared to those on tamoxifen/OFS, were higher by
19% (OR: 0.81, 95%CI 0.11-9.76, p=1), and 5 times the odds of females on tamoxifen alone (OR: 5.13, 95%CI 0.79-59.71, p=0.2). However, both associations did not reach statistical significance.

Regarding the administration of radiotherapy, there was no significant association between women on tamoxifen with or without OFS (OR: 0.25, 95%CI 0.05-1.14, p=0.13). On the contrary, women on AIs/OFS compared to those on monotherapy with tamoxifen were highly and significantly associated with the receipt of radiotherapy (OR is infinity, 95%CI 1.410-Infinity, p=0.031). Finally, an insignificant association was revealed compared to those treated with tamoxifen plus OFS (OR is infinity, 95%CI 0.349-Infinity, p=0.916).

Concerning treatment duration and ET, the distribution of participants is depicted in Figure 2. Generally, the relative frequencies were quite low for the classification of respondents in three different treatment periods. The possible significant association (p=0.019) between the two variables was most likely attributed to confounding and the small sample size.

![Figure 2](image-url)

**Figure 2**
The follow-up physician of choice was in most cases a medical oncologist (77.1%, N=54) and women appeared to be quite punctual with their annual gynecologist appointments (90%, N=63). Regarding discussions of women with their physicians about sexual health and problems, answers were quite divided. Nearly half of them (48.6%, N=34) pointed out that they rarely or never talk about these issues with their current physician, despite the fact that approximately 60% (N=41) admitted to a very or extremely affected sex life. Another 30% (N=21) would be more open to such conversations and frequently engage in those, while the rest 21.4% (N=15) would lie somewhere in the middle. However, thoughts about quitting the ET due to sexual problems would rarely or never occur in most participants (88.6%, N=62).

An important observation was the association of women in different ET groups with their subjective viewpoint of their sex life deterioration, which revealed a significant dependency. The outcome variable of deteriorated sex life resulted from a 4-point Likert-type scale and was handled as a continuous variable, with higher scores indicating greater intensity, therefore medians were calculated and the Mann-Whitney U test was applied in the pairwise comparisons between the ET groups. Responses of females on tamoxifen about their affected sexual activity did not differ significantly compared to respondents on tamoxifen plus OFS (p=1, medians and Q1, Q3 are presented in Table 5). Similarly, no statistically important difference was observed between women on tamoxifen compared to those on AIs. Nevertheless, women on AIs/OFS considered that their sex life had been negatively affected to a greater extent (median=4, Q1-Q3 [3;4]) compared to females on tamoxifen/OFS (median=2, Q1-Q3 [2;3]) and this difference was statistically significant (p=0.001).

<table>
<thead>
<tr>
<th>Comparison Groups (N=70)</th>
<th>Tamoxifen Group 1</th>
<th>Tamoxifen + OFS Group 2</th>
<th>AI + OFS Group 3</th>
<th>P values</th>
</tr>
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<tr>
<td></td>
<td>MD N=19</td>
<td>MD N=37</td>
<td>MD N=14</td>
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Variables: 20
<table>
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<tr>
<th>Age</th>
<th>Group 1 (45.47 ± 5.35)</th>
<th>Group 2 (42.68 ± 5.15)</th>
<th>Group 3 (47.71 ± 3.71)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>49.26 ± 3.4</td>
<td>&lt;0.001 *(Group 1,2)</td>
<td>0.987 *(Group 1,3)</td>
<td>0.002 *(Group 2,3)</td>
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</table>

<table>
<thead>
<tr>
<th>Marital status:</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Married (N=45, 64.3%)</td>
<td>14 (73.7%)</td>
<td>19 (51.4%)</td>
<td>12 (85.7%)</td>
<td>0.183 †</td>
</tr>
<tr>
<td>Divorced (N=7, 10%)</td>
<td>2 (10.5%)</td>
<td>4 (10.8%)</td>
<td>1 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>Single (N=15, 21.4%)</td>
<td>2 (10.5%)</td>
<td>12 (32.4%)</td>
<td>1 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>Widowed (N=2, 2.8%)</td>
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<td>2 (5.4%)</td>
<td>none</td>
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<tr>
<td>Other (N=1, 1.4%)</td>
<td>1 (5.3%)</td>
<td>none</td>
<td>none</td>
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</tr>
<tr>
<td>Children (Yes) (N=51, 72.9%)</td>
<td>14 (73.7%)</td>
<td>24 (64.9%)</td>
<td>13 (92.9%)</td>
<td>0.134 †</td>
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<table>
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<th>Educational Status:</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>p</th>
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</thead>
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<td>PE (N=1, 1.4%)</td>
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<td>6 (31.6%)</td>
<td>5 (13.5%)</td>
<td>1 (7.1%)</td>
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<tr>
<td>LSE (N=15, 21.4%)</td>
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<td>1 (5.3%)</td>
<td>3 (8.1%)</td>
<td>2 (14.3%)</td>
</tr>
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<td>Education Level</td>
<td>USE (N=6, 8.6%)</td>
<td>VET (N=17, 24.3%)</td>
<td>Bachelor (N=22, 31.45)</td>
<td>Master/PHD (N=9, 12.9%)</td>
</tr>
<tr>
<td>-----------------</td>
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<td>------------------------</td>
</tr>
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<td>USE</td>
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<td>7 (36.8%)</td>
<td>3 (15.8%)</td>
<td>2 (14.3%)</td>
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<tr>
<td>VET</td>
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<td>13 (35.1%)</td>
<td>4 (10.8%)</td>
<td>2 (14.3%)</td>
</tr>
<tr>
<td>Bachelor</td>
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<td></td>
<td>2 (10.5%)</td>
<td></td>
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<td>Employment status:</td>
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<tr>
<td>Private Sec. (N=22, 31.4%)</td>
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<td>13 (35.1%)</td>
<td>4 (28.6%)</td>
<td></td>
</tr>
<tr>
<td>Public Sec. (N=14, 20%)</td>
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<td>5 (13.5%)</td>
<td>3 (21.4%)</td>
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</tr>
<tr>
<td>Self-employed (N=4, 5.7%)</td>
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<td>3 (8.1%)</td>
<td>1 (7.1%)</td>
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</tr>
<tr>
<td>Retired (N=5, 7.1%)</td>
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<td>2 (5.4%)</td>
<td>1 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>Unemployed (N=25, 35.7%)</td>
<td>6 (31.6%)</td>
<td>13 (35.1%)</td>
<td>5 (35.7%)</td>
<td></td>
</tr>
<tr>
<td>Cancer stage:</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>IDK (N=30, 42.9%)</td>
<td>4 (21.1%)</td>
<td>19 (51.4%)</td>
<td>1 (7.1%)</td>
<td>none</td>
</tr>
<tr>
<td>Carcinoma in situ (N=3, 4.3%)</td>
<td>2 (10.5%)</td>
<td>1 (2.7%)</td>
<td>7 (50%)</td>
<td></td>
</tr>
<tr>
<td>Stage I (N=9, 12.9%)</td>
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<td>1 (2.7%)</td>
<td>1 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>Stage II (N=17, 24.3%)</td>
<td>5 (26.3%)</td>
<td>8 (21.6%)</td>
<td>4 (28.6%)</td>
<td></td>
</tr>
<tr>
<td>Stage III (N=7, 10%)</td>
<td>1 (5.3%)</td>
<td>5 (13.5%)</td>
<td>1 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>HER2 + (N=11, 15.7%)</td>
<td>1 (5.3%)</td>
<td>4 (10.8%)</td>
<td>6 (42.9%)</td>
<td>0.004 †§</td>
</tr>
<tr>
<td>---------------------</td>
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<td>-----------</td>
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</tr>
<tr>
<td><strong>Type of surgery:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCS (N=12, 17.1%)</td>
<td>4 (21.1%)</td>
<td>7 (18.9%)</td>
<td>1 (7.1%)</td>
<td>0.174 †</td>
</tr>
<tr>
<td>BCS/Mast + LND (N=44, 62.9%)</td>
<td>8 (42.1%)</td>
<td>24 (64.9%)</td>
<td>12 (85.7%)</td>
<td></td>
</tr>
<tr>
<td>Mastectomy (N=6, 8.6%)</td>
<td>2 (10.5%)</td>
<td>3 (8.1%)</td>
<td>1 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>Mast/BR (N=8, 11.4%)</td>
<td>5 (26.3%)</td>
<td>3 (8.1%)</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td><strong>Radiotherapy receipt (N=57, 81.4%)</strong></td>
<td>11 (57.9%)</td>
<td>32 (86.5%)</td>
<td>14 (100%)</td>
<td>0.011 †</td>
</tr>
<tr>
<td><strong>Chemotherapy receipt (N=53, 75.7%)</strong></td>
<td>10 (52.6%)</td>
<td>31 (83.8%)</td>
<td>12 (85.17%)</td>
<td>0.030 †</td>
</tr>
<tr>
<td><strong>Duration:</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.019 †</td>
</tr>
<tr>
<td>&gt;3 m &amp; &lt;1 y (N=24, 34.3%)</td>
<td>9 (47.4%)</td>
<td>15 (40.5%)</td>
<td>1</td>
<td>none</td>
</tr>
<tr>
<td>1-3 y (N=26, 37.1%)</td>
<td>5 (26.3%)</td>
<td>12 (32.4%)</td>
<td>9 (64.3%)</td>
<td></td>
</tr>
<tr>
<td>&gt;3 y (N=27.1%)</td>
<td>5 (26.3%)</td>
<td>10 (27%)</td>
<td>4 (28.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Family cancer (+) (N=25, 35.7%)</strong></td>
<td>6 (31.6%)</td>
<td>14 (37.8%)</td>
<td>5 (35.7%)</td>
<td>1 †§</td>
</tr>
<tr>
<td><strong>Genetic testing performed (N=23, 32.9%)</strong></td>
<td>9 (47.4%)</td>
<td>10 (27%)</td>
<td>4 (28.6%)</td>
<td>0.327 †§</td>
</tr>
<tr>
<td></td>
<td>4 (21.1%)</td>
<td>2 (5.4%)</td>
<td>3 (21.4%)</td>
<td>0.098 †§</td>
</tr>
<tr>
<td>------------------------------------</td>
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</tr>
<tr>
<td><strong>Antidepressant treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N=9, 12.9%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>5 (26.3%)</td>
<td>15 (40.5%)</td>
<td>4 (28.6%)</td>
<td>0.528 †</td>
</tr>
<tr>
<td>(N=24, 34.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Follow-up care physician:</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.148 †</td>
</tr>
<tr>
<td><strong>Breast surgeon</strong></td>
<td>6 (31.6%)</td>
<td>6 (16.2%)</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>(N=12, 17.1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medical oncologist</strong></td>
<td>12 (63.2%)</td>
<td>29 (78.4%)</td>
<td>13 (92.9%)</td>
<td></td>
</tr>
<tr>
<td>(N=54, 77.1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>1 (5.3%)</td>
<td>2 (5.4%)</td>
<td>1 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>(N=4, 5.7%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gynecologist visits</strong></td>
<td>3 [3;4]  ¥</td>
<td>4 [3;4]  ¥</td>
<td>3 [3;3.75]  ¥</td>
<td>0.439 ®</td>
</tr>
<tr>
<td><em>(3[3;4] ¥:</em></td>
<td>3 (15.8%)</td>
<td>6 (16.2%)</td>
<td>1 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>&gt;2 times a year</td>
<td>5 (26.3%)</td>
<td>15 (40.5%)</td>
<td>3 (21.4%)</td>
<td></td>
</tr>
<tr>
<td><em>(N=10, 14.3%)</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>once every 6 m</td>
<td>9 (47.4%)</td>
<td>15 (40.5%)</td>
<td>9 (64.3%)</td>
<td></td>
</tr>
<tr>
<td><em>(N=23, 32.9%)</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>once a year</td>
<td>1 (5.3%)</td>
<td>1 (2.7%)</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td><em>(N=33, 47.1%)</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rarely <em>(N=3, 4.3%)</em></td>
<td>1 (5.3%)</td>
<td>none</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>Never <em>(N=1, 1.4%)</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sexual problems discussion</strong></td>
<td>2 [1;4]  ¥</td>
<td>3 [2;4]  ¥</td>
<td>3 [2.3]  ¥</td>
<td>0.789 ®</td>
</tr>
<tr>
<td><em>(3 [1.25;4] ¥:</em></td>
<td>2 (10.5%)</td>
<td>2 (5.4%)</td>
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</tr>
<tr>
<td>Very frequently</td>
<td>5 (26.3%)</td>
<td>10 (27%)</td>
<td>2 (14.3%)</td>
<td></td>
</tr>
<tr>
<td><em>(N=4, 5.7%)</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequently</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Occasionally</td>
<td>Rarely</td>
<td>Very rarely or never</td>
<td></td>
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<tr>
<td>----------------------</td>
<td>--------------</td>
<td>--------</td>
<td>----------------------</td>
<td></td>
</tr>
<tr>
<td>(N=17, 24.3%)</td>
<td>2 (10.5%)</td>
<td>4 (21.1%)</td>
<td>6 (31.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 (18.9%)</td>
<td>9 (24.3%)</td>
<td>9 (24.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 (42.9%)</td>
<td>3 (21.4%)</td>
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### Sex life deterioration

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<th>Extremely</th>
<th>Very</th>
<th>Slightly</th>
<th>Not at all</th>
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<td>(N=18, 25.7%)</td>
<td>5 (26.3%)</td>
<td>4 (10.8%)</td>
<td>4 (21.1%)</td>
<td>4 (21.1%)</td>
</tr>
<tr>
<td></td>
<td>6 (31.6%)</td>
<td>14 (37.8%)</td>
<td>9 (64.3%)</td>
<td>9 (24.3%)</td>
</tr>
<tr>
<td></td>
<td>2 (10.5%)</td>
<td>1 (2.7%)</td>
<td>1 (7.1%)</td>
<td>1 (2.7%)</td>
</tr>
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### ET discontinuation

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<th>Frequently</th>
<th>Occasionally</th>
<th>Rarely</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=2, 2.9%)</td>
<td>1 (5.3%)</td>
<td>none</td>
<td>2 (10.5%)</td>
<td>3 (15.8%)</td>
</tr>
<tr>
<td>(N=0)</td>
<td></td>
<td>none</td>
<td>3 (8.1%)</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>none</td>
<td>1 (7.1%)</td>
<td>2 (14.3%)</td>
</tr>
</tbody>
</table>

**Significance Levels:**
- 0.004 *
- 0.664 *

The distribution of our two stratification variables (age and chemotherapy administration) in our study population are shown in **Figure 3 and 4**.

![Histogram of age](image)

*Figure 3 Histogram of age*
Age stratification (≤40 years and >40 years) resulted in two groups, with women of 40 years of age or under making up 18.6% of our sample (N=13, 37.08 ± 2.3), while women over 40 years old comprised the rest 81.4% (N=57, 47.39 ± 3.7). When participants were stratified according to age and chemotherapy receipt, 4 groups were formed: 21.4% (N=15) represented women >40 years old who did not receive chemotherapy, 60% (N=42) were women >40 that were administered chemotherapy, 15.7% were those ≤40 years of age who were treated with chemotherapy and only 2.9% (N=2) belonged in the younger age category and had not received adjuvant chemotherapy (Figure 5).
However, due to our small sample and the lack of responses from women ≤40 years of age on either tamoxifen alone or AI plus OFS (zero respondents on both categories), age stratification was not deemed applicable. Instead, we decided to involve age, as a continuous variable in our multivariate regression analysis.

Likewise, chemotherapy was administered in the majority of our respondents (N=53, 75.7%). Participant allocation in three different ET groups and stratification according to chemotherapy administration is demonstrated in Figure 6.

Figure 5 Age and chemotherapy stratification
Figure 6 Comparison groups (stratified for chemotherapy administration)

Group sizes after stratification were again not powered enough to predict significant differences and correlations, especially regarding participants who did not receive...
chemotherapy. Therefore, in our pilot study, stratification was not applied and the variables of age and chemotherapy was investigated in multivariate analysis.

**Sexual dysfunction**

Sexual functioning, our primary outcome, was assessed using two instruments, FSFI and QLQ-BR23.

**QLQ-BR23**

No missing values were encountered regarding the items for the functional scales of the QLQ-BR23, used in our analysis. Summary measures for the functional scales of the QLQ-BR23 are presented in Table 6-8. Distribution of scores for the scale of sexual functioning and sexual enjoyment are also depicted in Figure 7 and 8. In both scales, women on tamoxifen with and without OFS had the same median scores, thus no important difference was anticipated.

<table>
<thead>
<tr>
<th>Tamoxifen N=19</th>
<th>NA*</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>IQR</th>
<th>Min</th>
<th>Max</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual functioning</td>
<td></td>
<td>32.46</td>
<td>33.33</td>
<td>19.62</td>
<td>16.67</td>
<td>0</td>
<td>66.67</td>
<td>22.99 – 41.91</td>
</tr>
<tr>
<td>Sexual enjoyment</td>
<td>6</td>
<td>58.97</td>
<td>66.67</td>
<td>19.97</td>
<td>33.33</td>
<td>33.33</td>
<td>100</td>
<td>46.90 – 71.04</td>
</tr>
<tr>
<td>Body Image</td>
<td></td>
<td>64.91</td>
<td>75</td>
<td>33.86</td>
<td>25</td>
<td>0</td>
<td>100</td>
<td>48.59 – 81.23</td>
</tr>
<tr>
<td>Future perspective</td>
<td></td>
<td>42.11</td>
<td>33.33</td>
<td>38.24</td>
<td>66.67</td>
<td>0</td>
<td>100</td>
<td>23.67 – 60.53</td>
</tr>
</tbody>
</table>

*Table 6 QLQ-BR23 Functional Scale Scores of women on tamoxifen, * NA: not available due to no sexual activity

<table>
<thead>
<tr>
<th>Tamoxifen + OFS N=37</th>
<th>NA*</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>IQR</th>
<th>Min</th>
<th>Max</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual functioning</td>
<td></td>
<td>32.43</td>
<td>33.33</td>
<td>28.58</td>
<td>50</td>
<td>0</td>
<td>100</td>
<td>22.90 – 41.96</td>
</tr>
</tbody>
</table>
Table 7 QLQ-BR23 Functional Scale Scores of women on tamoxifen/OFS, * NA: not available due to no sexual activity

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>IQR</th>
<th>Min</th>
<th>Max</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual functioning</td>
<td>17.86</td>
<td>16.67</td>
<td>21.15</td>
<td>29.17</td>
<td>0</td>
<td>66.67</td>
<td>5.64 – 30.06</td>
</tr>
<tr>
<td>Sexual enjoyment</td>
<td>6</td>
<td>25</td>
<td>34.5</td>
<td>33.33</td>
<td>0</td>
<td>100</td>
<td>-3.84 – 53.84</td>
</tr>
<tr>
<td>Body Image</td>
<td>49.4</td>
<td>45.83</td>
<td>33.25</td>
<td>52.08</td>
<td>0</td>
<td>100</td>
<td>30.20 – 68.60</td>
</tr>
<tr>
<td>Future perspective</td>
<td>30.95</td>
<td>33.33</td>
<td>33.24</td>
<td>58.33</td>
<td>0</td>
<td>100</td>
<td>11.75 – 50.14</td>
</tr>
</tbody>
</table>

Table 8 QLQ-BR23 Functional Scale Scores of women on AI/OFS, * NA: not available due to no sexual activity

Figure 7 QLQ-BR23 Sexual Functioning scale in women on ET
Figure 8 QLQ-BR23 Sexual Enjoyment scale in women on ET

Among the three groups of ET, those on AI/OFS demonstrated worse scores in both sexual functioning and enjoyment scales (16.67, IQR=29.17, 95%CI [5.64;30.06] and 16.67, IQR=33.33, 95%CI [-3.94;53.84], respectively) compared to females on tamoxifen monotherapy (33.33, IQR=16.67, 95%CI [22.99;41.91] and 66.67, IQR=33.33, 95%CI [46.90;71.04], respectively) and those on tamoxifen/OFS (33.33, IQR=50, 95%CI [22.90;41.96] and 66.67, IQR=33.33, 95%CI [48.75;70.68], respectively). We applied Kruskal-Wallis test to investigate whether these differences were meaningful. No statistically significant difference was detected considering sexual functioning (p=0.127). However, the differences in median scores for the sexual enjoyment scale were important (p=0.014). According to pairwise comparisons that followed using the Mann-Whitney test with Bonferroni correction, females on AI/OFS appeared to derive less enjoyment from their sexual activity compared to those on tamoxifen with or without OFS (p=0.019 and p=0.020, respectively), while no difference was demonstrated among the two groups of women on tamoxifen (p=1). Comparisons for the scales of Body image and Future perspective did not produce any statistically significant results (p=0.288 and p=0.699, respectively, using Kruskal-Wallis test).
FSFI

Missing data of the FSFI items were approximately 5.7%, as 4 out of 70 respondents did not answer any of the FSFI items, therefore a complete case analysis was performed. The missing data pattern is demonstrated in Graph 1.

Graph 1

Summary measures for the FSFI domains are presented in Table 9-11.

<table>
<thead>
<tr>
<th>Tamoxifen</th>
<th>MD</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>IQR</th>
<th>Min</th>
<th>Max</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desire</td>
<td>1</td>
<td>2.67</td>
<td>2.4</td>
<td>1.24</td>
<td>1.8</td>
<td>1.2</td>
<td>5.4</td>
<td>2.05 - 3.28</td>
</tr>
<tr>
<td>Arousal</td>
<td>1</td>
<td>2.87</td>
<td>3</td>
<td>1.72</td>
<td>2.25</td>
<td>0</td>
<td>5.4</td>
<td>2.01 – 3.72</td>
</tr>
<tr>
<td>Lubrication</td>
<td>1</td>
<td>2.73</td>
<td>3.15</td>
<td>1.97</td>
<td>2.85</td>
<td>0</td>
<td>6</td>
<td>1.75 – 3.71</td>
</tr>
<tr>
<td>Orgasm</td>
<td>1</td>
<td>3.51</td>
<td>4.8</td>
<td>2.33</td>
<td>3.8</td>
<td>0</td>
<td>6</td>
<td>2.35 – 4.66</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>1</td>
<td>3.76</td>
<td>4.2</td>
<td>2.01</td>
<td>3.4</td>
<td>0.4</td>
<td>6</td>
<td>2.75 – 4.75</td>
</tr>
<tr>
<td>Pain</td>
<td>1</td>
<td>2.42</td>
<td>2.8</td>
<td>2.1</td>
<td>3.6</td>
<td>0</td>
<td>6</td>
<td>1.37 – 3.46</td>
</tr>
<tr>
<td>-----------</td>
<td>---</td>
<td>------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>---</td>
<td>---</td>
<td>------------</td>
</tr>
<tr>
<td><strong>Full Scale Score</strong></td>
<td>1</td>
<td>17.96</td>
<td>19.95</td>
<td>9.96</td>
<td>12.63</td>
<td>1.9</td>
<td>31.6</td>
<td>13.00 – 22.91</td>
</tr>
</tbody>
</table>

*Table 9 FSFI scores for women on tamoxifen alone*

<table>
<thead>
<tr>
<th>Tamoxifen + OFS</th>
<th>MD</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>IQR</th>
<th>Min</th>
<th>Max</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=37</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desire</td>
<td>3</td>
<td>2.84</td>
<td>3</td>
<td>1.36</td>
<td>2.4</td>
<td>1.2</td>
<td>5.4</td>
<td>2.36 – 3.31</td>
</tr>
<tr>
<td>Arousal</td>
<td>3</td>
<td>2.67</td>
<td>2.55</td>
<td>2.1</td>
<td>4.42</td>
<td>0</td>
<td>6</td>
<td>1.94 – 3.40</td>
</tr>
<tr>
<td>Lubrication</td>
<td>3</td>
<td>3.04</td>
<td>3.15</td>
<td>2.2</td>
<td>4.2</td>
<td>0</td>
<td>6</td>
<td>2.26 – 3.80</td>
</tr>
<tr>
<td>Orgasm</td>
<td>3</td>
<td>3.09</td>
<td>4</td>
<td>2.32</td>
<td>4.8</td>
<td>0</td>
<td>6</td>
<td>2.28 – 3.90</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>3</td>
<td>3.68</td>
<td>4.6</td>
<td>2.13</td>
<td>4.4</td>
<td>0.4</td>
<td>6</td>
<td>2.94 – 4.42</td>
</tr>
<tr>
<td>Pain</td>
<td>3</td>
<td>3.31</td>
<td>4</td>
<td>2.48</td>
<td>5.8</td>
<td>0</td>
<td>6</td>
<td>2.44 – 4.17</td>
</tr>
<tr>
<td><strong>Full Scale Score</strong></td>
<td>3</td>
<td>18.63</td>
<td>20.8</td>
<td>11.59</td>
<td>21.85</td>
<td>1.6</td>
<td>34.6</td>
<td>14.58 – 22.67</td>
</tr>
</tbody>
</table>

*Table 10 FSFI scores for women on tamoxifen/OFS*

<table>
<thead>
<tr>
<th>AI + OFS</th>
<th>MD</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>IQR</th>
<th>Min</th>
<th>Max</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desire</td>
<td>1.67</td>
<td>1.2</td>
<td>0.79</td>
<td>0.6</td>
<td>1.2</td>
<td>3.6</td>
<td></td>
<td>1.21 – 2.12</td>
</tr>
<tr>
<td>Arousal</td>
<td>1.44</td>
<td>1.2</td>
<td>1.48</td>
<td>1.35</td>
<td>0</td>
<td>5.7</td>
<td></td>
<td>0.57 – 2.29</td>
</tr>
<tr>
<td>Lubrication</td>
<td>1.41</td>
<td>1.5</td>
<td>1.48</td>
<td>2.03</td>
<td>0</td>
<td>4.5</td>
<td></td>
<td>0.55 – 2.26</td>
</tr>
<tr>
<td>Orgasm</td>
<td>1.94</td>
<td>1.2</td>
<td>2.2</td>
<td>3.9</td>
<td>0</td>
<td>6</td>
<td></td>
<td>0.67 – 3.21</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>1.66</td>
<td>1.2</td>
<td>1.42</td>
<td>1.9</td>
<td>0.4</td>
<td>5.2</td>
<td></td>
<td>0.83 – 2.47</td>
</tr>
<tr>
<td>Pain</td>
<td>1.11</td>
<td>0.6</td>
<td>1.28</td>
<td>2</td>
<td>0</td>
<td>3.6</td>
<td></td>
<td>0.37 – 1.85</td>
</tr>
<tr>
<td><strong>Full Scale Score</strong></td>
<td>9.24</td>
<td>8.8</td>
<td>7.57</td>
<td>11.35</td>
<td>1.6</td>
<td>28</td>
<td></td>
<td>4.86 – 13.60</td>
</tr>
</tbody>
</table>

*Table 11 FSFI scores for women on AI/OFS*
Our population’s FSFI overall scores did not follow a normal distribution as depicted in Figure 9. According to Zachariou et al., scores under the cutoff value of 26 are indicative of sexual dysfunction in Greek females. (68) In our study population, 74.2% (N=49) had scores indicative of sexual dysfunction, with a median value of 17.45, IQR=26.18, revealing that women on endocrine treatment might be in serious risk regarding their sexual health (Figure 9). Particularly, women on AI/OFS had the lowest scores (median=8.8, IQR=11.35, 95%CI [4.86 – 13.60]), while females on tamoxifen with and without OFS had roughly the same median values (20.8, IQR=21.85 and 19.95, IQR=12.63, respectively). Boxplots of the overall scores for the three groups reveal the distribution of our data (Figure 10). The results of the comparisons that followed among the three study groups, for each domain of the FSFI, are presented in Table 12.

Figure 9
Figure 10

Table 12 Comparisons among the three study groups for the FSFI domains and Full Scale Score, *Kruskal-Wallis test
The comparisons for each domain of the FSFI questionnaire revealed statistically significant differences among women of the three study groups regarding Desire, Satisfaction and Pain, as well as the overall FSFI score. Consequently, we performed pairwise comparisons among the three groups (Table 13).

<table>
<thead>
<tr>
<th>Pairwise comparisons</th>
<th>Tamoxifen and Tam/OFS</th>
<th>Tamoxifen and AI/OFS</th>
<th>AI/OFS and TAM/OFS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P-value</strong> *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desire</td>
<td>1</td>
<td>0.031</td>
<td>0.016</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>1</td>
<td>0.016</td>
<td>0.017</td>
</tr>
<tr>
<td>Pain</td>
<td>0.423</td>
<td>0.187</td>
<td>0.017</td>
</tr>
<tr>
<td>Full Scale Score</td>
<td>1</td>
<td>0.039</td>
<td>0.040</td>
</tr>
</tbody>
</table>

*Table 13 Pairwise comparisons for the domains of Desire, Satisfaction, Pain and Overall score, *Mann-Whitney test with Bonferroni correction*

In summary, the differences in medians between the tamoxifen and AI/OFS groups in the domains of Desire (2.4, 95%CI [2.05;3.28] vs 1.2, 95%CI [1.21;2.12], p=0.031) and Satisfaction (3.76, 95%CI [2.75;4.75] vs 1.2, 95%CI [0.83;2.47], p=0.016) were statistically significant. Likewise, comparisons showed significant differences between women on AI/OFS and tamoxifen/OFS in the domains of Desire (1.2, 95%CI [1.21;2.12] vs 3, 95%CI [2.36;3.31], p=0.016), Satisfaction (1.2, 95%CI [0.83;2.47] vs 4.6, 95%CI [2.94;4.42], p=0.017) and Pain (0.6, 95%CI [0.37;1.85] vs 4, 95%CI [2.44;4.17], p=0.017). Regarding the FSFI Full Scale Score, in both comparisons of women on tamoxifen alone vs AI/OFS (19.95, 95%CI[13;22.91] vs 8.8, 95%CI [4.86;13.60], p=0.039) and those on tamoxifen/OFS vs AI/OFS (20.8, 95%CI[14.58;22.67] vs 8.8, 95%CI [4.86;13.60], p=0.040), scores were significantly lower, therefore indicating worse sexual functioning.
Gynecologic health and conditions

A brief set of questions about the gynecologic and obstetrics history was included in the second part of our questionnaire and a summary of the results is presented in Table 14. Specifically, over one third of the participants responded positively about the use of products for the symptoms of vaginal atrophy, such as lubricating creams and ointments (N=24, 34.3%), but no statistically significant difference was found among the three different ET groups. On the other hand, the use of products containing estradiol for the abovementioned reason, was much less popular (N=5, 7.1%).

<table>
<thead>
<tr>
<th>Participants</th>
<th>Tamoxifen</th>
<th>Tamoxifen + OFS</th>
<th>AI + OFS</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=70</td>
<td>MD N=19</td>
<td>MD N=37</td>
<td>MD N=14</td>
<td></td>
</tr>
<tr>
<td>Pregnancy discontinuation</td>
<td>6 (31.6%)</td>
<td>10 (27%)</td>
<td>6 (42.9%)</td>
<td>0.546†</td>
</tr>
<tr>
<td>Abortion 25 (35.7%)</td>
<td>7 (36.8%)</td>
<td>9 (24.3%)</td>
<td>9 (64.3%)</td>
<td>0.029◊</td>
</tr>
<tr>
<td>Cesarean Delivery 23 (32.9%)</td>
<td>4 (21%)</td>
<td>12 (32.4%)</td>
<td>7 (50%)</td>
<td>0.241†</td>
</tr>
<tr>
<td>Gynecologic surgery 3 (4.3%)</td>
<td>2 (10.5%)</td>
<td>1 (2.7%)</td>
<td>none</td>
<td>0.276†</td>
</tr>
<tr>
<td>Moisturizing/lubricating vaginal products 24 (34.3%)</td>
<td>7 (36.8%)</td>
<td>10 (27%)</td>
<td>7 (50%)</td>
<td>0.277†</td>
</tr>
<tr>
<td>Estradiol vaginal products 5 (7.1%)</td>
<td>none</td>
<td>4 (10.8%)</td>
<td>1 (7.1%)</td>
<td>0.389†</td>
</tr>
<tr>
<td>Transvaginal ultrasound 65 (92.9%)</td>
<td>14 (73.7%)</td>
<td>37 (100%)</td>
<td>14 (100%)</td>
<td>0.005†</td>
</tr>
</tbody>
</table>

*Table 14 Summary of results - Ob/Gyn history, † Fisher’s exact test, ◊ Chi^2 test*
Significant differences were only observed in two of our variables; history of abortion and transvaginal ultrasound examination. The dependency between history of abortion and the type of endocrine therapy was probably a result of confounding and was not further investigated as there are no data to support the hypothesis of a possible association between the two variables. On the other hand, a significant association regarding the transvaginal ultrasound examination was detected between women on tamoxifen monotherapy compared to those who were additionally treated with OFS. The latter, in particular, would have 100% higher odds of having been examined with a transvaginal ultrasound (OR:0, 95%CI 0-0.665, p=0.027).

A number of gynecologic conditions associated with the administration of ET and their manifestation after the initiation of these agents was also investigated. Briefly, our sample comprised mostly of females who had never been diagnosed with any of the gynecologic conditions in question (N=24, 34.3%). In contrast a 22.9% (N=16), reported problems both before and after initiation of treatment. Another 22.9% (N=16) reported at least one of the listed conditions, diagnosed before ET, but not after. To the contrary, a 20% (N=14) had a clear gynecologic history before, but this changed after treatment. Only a few cases of endometriosis and genital warts, just one ectopic pregnancy, as well as an individual case of STD or HPV infection, which were of no particular interest. In Table 15, the relative frequencies of specific conditions that have been associated with ET and manifested after treatment, are presented. Women who had been diagnosed with any of those before ET initiation were excluded from the analysis.

<table>
<thead>
<tr>
<th>Participants N=70</th>
<th>Tamoxifen</th>
<th>Tamoxifen + OFS</th>
<th>AI + OFS</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD N=19</td>
<td>MD N=37</td>
<td>MD N=14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N* (Relative frequencies %)</td>
<td>N* (Relative frequencies %)</td>
<td>N* (Relative frequencies %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gynecologic conditions after ET</td>
<td>Subjects with pre-treatment condition were excluded from the analysis, UGT: Urogenital Tract, † Fisher’s exact test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine/cervical fibroids *</td>
<td>none</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (3.4%)</td>
<td>1 (3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (10%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.383 †</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine/cervical polyps *</td>
<td>none</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (3%)</td>
<td>2 (5.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>none</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 †</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UGT infections *</td>
<td>3 (18.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 (20.8%)</td>
<td>5 (17.9%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (33.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.590 †</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian cysts</td>
<td>2 (10.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (2.9%)</td>
<td>none</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>none</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.109 †</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 15 Gynecologic conditions after ET. * Subjects with pre-treatment condition were excluded from the analysis, UGT: Urogenital Tract, † Fisher’s exact test

Overall, the absolute frequencies of these conditions after ET initiation were rather low regardless of the type of treatment and no statistically significant association was therefore detected. Urogenital tract infections occurred in nearly 20% of women with no prior history, after the initiation of ET. The highest frequency (N=3, 33%) was observed on females who received AI/OFS. Ovarian cysts manifested in only 2 of our respondents who had never been diagnosed before with this condition and they were both on tamoxifen at that time.

Furthermore, no case of endometrial cancer was detected in our population and only five women (7.1%) had undergone endometrial ablation, three of whom were treated with tamoxifen. Regarding endometrial thickness, while a substantial proportion of our respondents was not aware of their last measurement of endometrial thickness (N=30, 42.9%), roughly 16% (N=11) responded positively about having a measurement >5 mm, 10 of whom were women.
who were treated with tamoxifen with or without OFS (Figure 11). Accordingly, endometrial ablation was performed on 5 females from the tamoxifen groups. Two of our participants (2.9%) had been diagnosed with another gynecologic malignancy (cervical cancer in situ and ovarian cancer). Summary results for our comparison groups, as well as the index scores for vaginal atrophy symptoms are shown in Table 16 and 17.

Figure 11
<table>
<thead>
<tr>
<th>Participants</th>
<th>Tamoxifen</th>
<th>Tamoxifen + OFS</th>
<th>AI + OFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD or NA</td>
<td>N=19</td>
<td>MD or NA</td>
<td>N=37</td>
</tr>
<tr>
<td>N (Relative frequencies %)</td>
<td>N (Relative frequencies %)</td>
<td>N (Relative frequencies %)</td>
<td></td>
</tr>
<tr>
<td>Endometrial thickness &gt;5 mm</td>
<td>11 (15.7%)</td>
<td>9 (47.3%)</td>
<td>4 (21%)</td>
</tr>
<tr>
<td>Endometrial ablation</td>
<td>5 (7.1%)</td>
<td>1 (5.3%)</td>
<td>none</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>1 (5.3%)</td>
<td>none</td>
<td>1 (2.8%)</td>
</tr>
<tr>
<td>Other gynecologic malignancy</td>
<td>2 (2.9%)</td>
<td>1 (5.3%)</td>
<td>1 (2.8%)</td>
</tr>
</tbody>
</table>

Table 16 Gynecologic health complications among ET groups, MD: Missing Data, NA: Not Available, * Mean ± standard deviations, † Fisher’s exact test
<table>
<thead>
<tr>
<th>Vaginal atrophy symptoms</th>
<th>Median (IQR)</th>
<th>Median (IQR)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal bleeding</td>
<td>1 (5.3%)</td>
<td>1 (5.3%)</td>
<td>6 (16.2%)</td>
</tr>
<tr>
<td>Vaginal secretions</td>
<td>11 (57.9%)</td>
<td>12 (32.4%)</td>
<td>3 (21.4%)</td>
</tr>
<tr>
<td>Unpleasant odor</td>
<td>6 (31.6%)</td>
<td>12 (32.4%)</td>
<td>6 (42.9%)</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>3 (3)</td>
<td>1 (2)</td>
<td>3.5 (4)</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>3 (1.5)</td>
<td>3 (1)</td>
<td>3.5 (2.5)</td>
</tr>
<tr>
<td>Vaginal pruritus</td>
<td>3 (2.75)</td>
<td>2 (2)</td>
<td>2.5 (1.75)</td>
</tr>
<tr>
<td>Vaginal redness</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>1.5 (2)</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>2 (2)</td>
<td>2 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>VAI</td>
<td>2.43 ± 0.82 ¥</td>
<td>2.07 ± 0.65 ¥</td>
<td>2.3 ± 1.06 ¥</td>
</tr>
</tbody>
</table>

Table 17 Vaginal atrophy symptoms among ET groups, MD: Missing Data, NA: Not Available, VAI: Vaginal Atrophy Index, * Chi^2 test, † Fisher’s exact test, ¥ Mean ± standard deviations, ® Kruskal-Wallis test
Missing data were extremely low, counting just 4 values (0.7%) among all items that assessed vaginal atrophy symptoms. Of all the vaginal symptoms that were evaluated regarding their manifestation or frequency, an association which was borderline insignificant was detected among the different types of ET and vaginal dryness, with women on AI/OFS presenting such symptoms more often (median:3.5, IQR=2.5), compared to the other groups (p=0.058).

Regarding increase of vaginal discharge, a high proportion of women who received tamoxifen with or without OFS, responded positively, compared to just 21.4% of women on AI/OFS. However, the association of vaginal discharge with the type of ET was again borderline insignificant (p=0.058).

The following histogram and boxplots demonstrate distribution of overall scores in our sample and comparison groups (Figure 12 and 13). The median value of VAI for our population was 2.25 and represented moderate frequency of vaginal atrophy symptoms, with IQR 1.25, minimum and maximum scores 1 and 3.62, respectively. A descriptive summary of this variable for our three comparison groups is presented in Table 18.
Figure 13

Table 18 Summary measures of vaginal atrophy index, CI: Confidence Interval * Student’s t-test with Welch and Bonferroni correction
According to the mean scores of VAI across the three groups, women who received tamoxifen alone had the highest scores and along with those on AI/OFS, their symptoms were considered frequent, while those on the tamoxifen/OFS group had a borderline frequent to rare manifestation. The tests of normality (Shapiro-Wilk test) and the boxplots indicated that the scores in each of our three ET groups were normally distributed, however the Levene’s test revealed that the variances of our three groups were not equal (p=0.0215). Due to heteroscedasticity we decided to apply Welch’s correction in our consequent pairwise comparisons. No statistically significant difference was detected regarding VAI among our three comparison groups. It should also be noted that our study demonstrated a moderate internal consistency of the questions considering vaginal atrophy of 0.64 (95%CI [0.52;0.77]), according to Cronbach’s alpha coefficient.

**UDI-6 and PFIQ-7**

Missing data of the UDI-6 and PFIQ-7 items are presented in **Graph 2.** Briefly, in 90% of the aforementioned items there are no missing values, while the range of missing values in each question is 2.9-5.7%. Missing data were imputed using simple random imputation.

*Graph 2 Missing data plot of the UDI-6 and PFIQ-7 items*
Summary measures of the scores are shown in Table 19-21. The median score for Urinary Distress Index was 31.25, IQR=32.39 (95%CI 26.10-36.87) for our whole sample. Generally, higher scores represented higher disability. Among the three groups, the highest score was observed in women on AI/OFS with a mean value of 38.39 ± 27.01, followed by the tamoxifen group at 37.06 ± 24.45. Women on tamoxifen/OFS had milder symptoms, with a mean score of 25.45 ± 18.55.

<table>
<thead>
<tr>
<th>UDI-6 Score</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Q1</th>
<th>Q3</th>
<th>IQR</th>
<th>Min</th>
<th>Max</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population N=70</td>
<td>31.49</td>
<td>31.25</td>
<td>22.59</td>
<td>16.67</td>
<td>48.96</td>
<td>32.39</td>
<td>0</td>
<td>87.5</td>
<td>26.10-36.87</td>
</tr>
<tr>
<td>Tamoxifen N=19</td>
<td>37.06</td>
<td>41.67</td>
<td>24.45</td>
<td>18.75</td>
<td>50</td>
<td>31.25</td>
<td>0</td>
<td>87.5</td>
<td>25.28-48.85</td>
</tr>
<tr>
<td>Tamoxifen/OFS N=37</td>
<td>25.45</td>
<td>25</td>
<td>18.55</td>
<td>8.33</td>
<td>37.5</td>
<td>29.17</td>
<td>0</td>
<td>62.5</td>
<td>19.26-31.63</td>
</tr>
<tr>
<td>AI/OFS N=14</td>
<td>38.39</td>
<td>39.58</td>
<td>27.01</td>
<td>16.67</td>
<td>61.46</td>
<td>44.79</td>
<td>0</td>
<td>75</td>
<td>22.79-53.98</td>
</tr>
<tr>
<td>Pairwise comparisons</td>
<td>Tamoxifen and Tam/OFS</td>
<td>Tamoxifen and AI/OFS</td>
<td>AI/OFS and TAM/OFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value *, 95% CI</td>
<td>0.169</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.392</td>
<td></td>
</tr>
</tbody>
</table>

Table 19 Summary measures of UDI-6 score, CI: Confidence Interval, * Student’s t-test with Welch and Bonferroni correction

The following histograms represent the distribution of UDI-6 values in the three study groups, which demonstrate an approximately normal distribution (Figure 14).
As mentioned before, due to the homoscedasticity of our data, we performed pairwise comparisons with t-test and Welch’s correction. As anticipated, no statistically significant difference in urinary symptoms was demonstrated between our study groups.

The scores for the PFIQ-7 items (Table 20) that assessed the impact of urinary symptoms on quality of life were generally low, with a median value of 9.52/100, IQR=22.62 for our study population. The highest scores were observed, as expected, in the AI/OFS group with a median value of 19.05, IQR= 34.52, 95%CI (12.64-45.17).
<table>
<thead>
<tr>
<th>PFIQ-7 Bladder/Urine Score</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Q1</th>
<th>Q3</th>
<th>IQR</th>
<th>Min</th>
<th>Max</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population N=70</td>
<td>16.60</td>
<td>9.52</td>
<td>21.32</td>
<td>0</td>
<td>22.62</td>
<td>22.62</td>
<td>0</td>
<td>100</td>
<td>11.51 – 21.68</td>
</tr>
<tr>
<td>Tamoxifen N=19</td>
<td>15.04</td>
<td>4.76</td>
<td>22.24</td>
<td>0</td>
<td>19.05</td>
<td>19.05</td>
<td>0</td>
<td>76.2</td>
<td>4.31 – 25.75</td>
</tr>
<tr>
<td>AI/OFS N=14</td>
<td>28.91</td>
<td>19.05</td>
<td>28.17</td>
<td>9.52</td>
<td>44.05</td>
<td>34.52</td>
<td>0</td>
<td>100</td>
<td>12.64 – 45.17</td>
</tr>
<tr>
<td>P-value *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.067</td>
</tr>
</tbody>
</table>

*Table 20 Summary measures of PFIQ-7 score for bladder/urine, CI: Confidence Interval, *Kruskal-Wallis test*

In **Figure 15**, graphical normality assessment of the distribution of PFIQ values for urinary symptoms’ impact, indicated that the data were not normally distributed. We performed the Kruskal-Wallis test, with the null hypothesis that participants of the three study groups had the same distribution of their scores in the population. The test resulted in a p value=0.067, therefore the medians of the three groups did not differ significantly.
Figure 15

Similarly, the median value of our population for the pelvic organ impact was very low at 7.14, IQR=19.05 (Table 21), while women on AI/OFS exhibited relatively higher scores (median=14.29, IQR=36.90).

<table>
<thead>
<tr>
<th>PFIQ-7 Vaginal/Pelvis Score</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Q1</th>
<th>Q3</th>
<th>IQR</th>
<th>Min</th>
<th>Max</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population N=70</td>
<td>12.93</td>
<td>7.14</td>
<td>18.89</td>
<td>0</td>
<td>19.05</td>
<td>19.05</td>
<td>0</td>
<td>100</td>
<td>8.42 – 17.43</td>
</tr>
<tr>
<td>Tamoxifen N=19</td>
<td>9.77</td>
<td>4.76</td>
<td>11.28</td>
<td>0</td>
<td>19.05</td>
<td>19.05</td>
<td>0</td>
<td>28.57</td>
<td>4.34 – 15.21</td>
</tr>
</tbody>
</table>
Table 21 Summary measures of PFIQ-7 score for vagina/pelvis, CI: Confidence Interval * Kruskal-Wallis test

The distributions of values for the PFIQ-7 items for pelvic organ impact in the three study groups, as demonstrated in Figure 16, were positively skewed. We applied Kruskal-Wallis test to investigate if the distributions were similar, which resulted in non-statistically significant differences (p=0.106).

Figure 16
**Multivariable regression analysis**

In our univariate analysis, a significant association between the three different endocrine therapies and the female sexual functioning was detected. However, further research was necessary to detect for confounding factors and effect modification. Therefore, we decided to investigate our primary outcome, represented by the overall score of the FSFI, and its association with the independent variables of age, marital and occupational status, chemotherapy administration, ET treatment and treatment duration.

Only the variables of chemotherapy administration and ET satisfied the assumptions for linear regression. The following table summarizes the results of the univariate and multivariate linear regression (Table 2).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted $\beta$</td>
<td>95%CI</td>
</tr>
<tr>
<td>Chemotherapy (No/Yes)</td>
<td>8.678</td>
<td>(2.572,14.782)</td>
</tr>
<tr>
<td>Tamoxifen/AI + OFS</td>
<td>8.720</td>
<td>(1.283,16.156)</td>
</tr>
<tr>
<td>Tamoxifen + OFS/AI + OFS</td>
<td>9.397</td>
<td>(2.769,16.023)</td>
</tr>
</tbody>
</table>

*Table 2 Linear regression univariate analysis results for effect on FSFI score, $\beta$: coefficient of the explanatory variable*

According to our first model, the $\beta_0$ coefficient was estimated at 14.48, 95%CI [11.571;17.392]) and the coefficient for chemotherapy administration was 8.678, 95%CI [2.572;14.782], which was interpreted as the change in the FSFI overall score when women did not undergo chemotherapy and this raise in the FSFI score was significant (p=0.006). Regarding the different agents of ET, $\beta_0$ coefficient was 9.236, meaning that women on tamoxifen alone exhibited a statistically important increase of 8.720, 95%CI [1.283;16.156] in their FSFI score, compared to
women on AI/OFS (p=0.022). Respectively, the increase for females on tamoxifen/OFS was 9.397, 95%CI [2.769;16.023], p=0.006.

However, according to our multivariable regression analysis of the participants’ FSFI scores on chemotherapy administration and ET, we noticed that the coefficient of chemotherapy administration increased, while the coefficients for the ET agents decreased. Therefore, avoidance of chemotherapy would increase sexual functioning by 8.838, 95%CI [2.718;14.957], as adjusted for the different ET, and this result was statistically important (p=0.005). Interestingly, the coefficient for the women on tamoxifen alone demonstrated the greatest decrease and did not maintain its statistical significance.

Summarized results of a second analysis in a smaller subgroup of our participants (N=45,) that included only those that responded positively to having sexual activity in the previous four weeks, is depicted in Table 23. All assumptions for linear regression were met. For our multivariable model we selected variables <0.2. However, due to the small size of this subset of respondents, only 4 variables were selected, that were considered as most important for investigation.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted β</td>
<td>95%CI</td>
</tr>
<tr>
<td>Tamoxifen/AI + OFS</td>
<td>7.691</td>
<td>(1.030, 14.352)</td>
</tr>
<tr>
<td>Tamoxifen + OFS/AI + OFS</td>
<td>11.855</td>
<td>(5.770, 17.939)</td>
</tr>
<tr>
<td>Body image score</td>
<td>0.091</td>
<td>(0.020, 0.162)</td>
</tr>
<tr>
<td>Future perspective score</td>
<td>0.047</td>
<td>(-0.021, 0.114)</td>
</tr>
</tbody>
</table>
Table 23 Linear regression univariate analysis results for effect on FSFI score for women sexually active the previous 4 weeks, β: coefficient of the explanatory variable

<table>
<thead>
<tr>
<th>Exploratory variable</th>
<th>β (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.158</td>
<td>0.536</td>
</tr>
<tr>
<td>Chemotherapy (No/Yes)</td>
<td>1.891 (-3.647, 7.430)</td>
<td>0.495</td>
</tr>
<tr>
<td>Duration (&gt;3 years/≤3 years)</td>
<td>-0.267 (-5.836, 5.302)</td>
<td>0.923</td>
</tr>
<tr>
<td>Single/Married</td>
<td>1.845 (-5.356, 9.046)</td>
<td>0.607</td>
</tr>
<tr>
<td>Divorced/Married</td>
<td>6.017 (-3.115, 15.148)</td>
<td>0.191</td>
</tr>
<tr>
<td>Other/Married</td>
<td>4.517 (-5.871, 14.905)</td>
<td>0.385</td>
</tr>
<tr>
<td>Unemployed or retired/Employed</td>
<td>3.358 (-1.932, 8.648)</td>
<td>0.207</td>
</tr>
</tbody>
</table>

All coefficients were decreased and the effect of all except one of our explanatory variables on FSFI scores, was determined as insignificant. Nevertheless, when adjusted for body image and future perspective scores, women on tamoxifen/OFS manifested significant increase in their estimated FSFI score compared to those on AI/OFS (β1=10.773, 95%CI [4.705;16.839], p <0.001).

Discussion

Although participation was not adequate to allow us to proceed with our original protocol and the predefined analyses, our study’s preliminary results clearly demonstrated the magnitude and complexity of problems associated with the sexual and gynecologic health of premenopausal women on adjuvant ET for breast cancer. Our questionnaire was quite extended, with more than 100 questions, most of which would pertain to sensitive information.
about sexuality and problems of the female reproductive system. Despite it being both time-consuming and at times even stressful, as few of our participants mentioned afterwards, a satisfactory number of respondents fully completed it, as indicated by the low rates of missing values (~4%).

Respondents were distributed in three groups according to the type of ET they were receiving. Most of them were treated with tamoxifen plus OFS (N=37, 52.9%), while females on tamoxifen monotherapy (N=19, 27.1%) and AI plus OFS (N=14, 20%) were fewer. This discrepancy was anticipated, as these women usually represent patients with straightforward features for estimation of their individual risk for recurrence, on which the choice of treatment depends. (81) However, in most cases the risk is intermediate. Similar issues were encountered regarding age and chemotherapy administration, as these are strongly associated in women with breast cancer. Therefore, our study population was insufficient in order to be stratified, as females under the age of 40 comprised 18.6% of our sample (N=13, 37.08 ± 2.3) and the mean age of patients on the tamoxifen/OFS group was significantly lower than the rest of the groups (42.68 ± 5.15). Likewise, 75.7% of the participants had received prior chemotherapy, which is much higher than the 55% of patients in the SOFT trial. Particularly, the percentage of women in both age groups who did not undergo chemotherapy was low compared to those who received chemotherapy (2.9% vs 15.7% for women ≤ 40 and 21.4% vs 60% for women >40, respectively) and this is an indirect indication of the current practice in Greece.

More than half of our respondents (N=41, 58.6%) reported that their sex life had been greatly affected after initiation of ET. However, only a small proportion of these women (N=21, 30%) would discuss on a frequent basis or be informed about these issues by their treating physician. These results are consistent with previous studies, which estimate that less than half of the female patients engage in such discussions, are medically evaluated or offered treatment solutions. (82,83) This substantive failure of our healthcare system to guide female cancer survivors and address to their needs with respect to both physical and quality of life issues, is associated with the current socioeconomic status, the lack of proper education and awareness
by the healthcare providers, as well as the absence of organized facilities, specialized in cancer patients, where they can be referred to for individualized management.

Our study’s main findings regarding sexual functioning, not only revealed the impact of adjuvant ET on it, but also associated the type of treatment with the level of dysfunction, therefore confirming our hypothesis. In particular, women on aromatase inhibitors concurrent with OFS experienced a significant decline in their sexual functioning to a greater extent compared to women on monotherapy with tamoxifen (8.8, 95%CI [4.86;13.60] vs 19.95, 95%CI [13;22.91] respectively, p=0.039). This difference was mostly evident in the domains of desire and satisfaction. Sexual enjoyment, as assessed by an additional instrument, was also decreased in this group of patients, compared to women on tamoxifen with or without OFS (p=0.019 and p=0.020, respectively). Comparisons of women on AI/OFS versus tamoxifen/OFS yielded in all cases worse results for the first subgroup of patients (8.8, 95%CI [4.86;13.60] vs 20.8, 95%CI [14.58;22.67] respectively, p=0.040). Sexual enjoyment and satisfaction, desire and pain, were all significantly affected in women who received aromatase inhibitors. In a subset of our population including only sexually active females, other factors, such as administration of chemotherapy, the woman’s negative perception of body image or distress about the future, were investigated as possible contributors to the overall sexual dysfunction. The difference, however, among the two groups remained significant, despite adjustments to these factors (p<0.001).

These findings, even though further analyses in a larger sample would allow more thorough investigation of other variables and possibly produce more rogue results, indicate that women on AIs are in higher risk of sexual dysfunction, as a result of decreased libido and pain experienced during sexual intercourse. Our results are in accordance with the outcomes of the SOFT and TEXT trials that report the greatest burden of sexual dysfunction in women on exemestane plus OFS. (84) Interestingly, among our respondents, women on AIs reported that the decline on their sex life after treatment with these agents was considerably worse compared to what women on tamoxifen/OFS responded. Therefore, healthcare professionals should extensively inform and educate their patients in advance about these implications,
discuss the ET options, engage them in decision-making, as well as elaborate on a management plan for arising sexual problems related to the ET.

We did not manage to detect a statistically significant difference regarding sexual functioning in women with or without OFS (20.8, IQR=21.85 and 19.95, IQR=12.63), as stated in former studies. (84–86) This could probably be attributed to our study not being adequately powered. For potentially similar reasons, our research regarding the incidence of several gynecologic conditions that have been associated with these treatments did not result in statistically significant differences. A finding worth-mentioning, perhaps, is that 5.1% (N=7) of our respondents had undergone endometrial ablation, all of whom had been treated with tamoxifen with or without OFS. Although a causal relationship between tamoxifen and endometrial hyperplasia exists, no statistically important difference was found among the three groups. (87)

Symptoms of vaginal atrophy, like vaginal discharge, dyspareunia and vaginal dryness were also under investigation. Previous research had shown that vaginal dryness was prominent in women on AI/OFS compared to those on tamoxifen and this was also confirmed in our sample, with the respective group of women reporting a moderate to high frequency of this condition (median=3.5, IQR=2.5). On the other hand, vaginal discharge would mostly affect women on tamoxifen monotherapy, as reported by 57.9% (N=11) of this group of females. However, in our study frequency rather than intensity of symptom was investigated, compared to the SOFT and TEXT trials. (84) These observations were both borderline insignificant (p=0.058 in both comparisons). Despite the possible side effects experienced by our participants, only a 34% (N=24) and a much smaller (7.1%, N=5) part of them would use lubricating and vaginal estradiol products, respectively. It should be noted though, that half the women treated with AI/OFS reported positively regarding application of moisturizing products, which is probably associated with the higher prevalence of vaginal dryness in this population.

Limitations
Our study’s primary limitation is the divergence from the original protocol, as our sample’s inadequate size, due to slow accrual, did not allow us to proceed with the predefined sample stratification, subgroup analysis and multivariate regression. Therefore, all results should be interpreted with caution, as possible confounding and effect modification might have interfered with our outcomes. Another argument would be the presence of selection bias, as women who were interested and decided to participate in our study would most probably be the ones who had experienced the side effects of the respective endocrine therapy. This would cause distortion in our analysis and artificially enlarge the effect. Consequently, our study outcomes are not easily generalizable to the population. As far as our questionnaire’s structure is concerned, assessment of internal consistency for the items regarding the symptoms of vaginal atrophy yielded a rather questionable level of reliability, according to Cronbach’s alpha estimation (0.64). Finally, concerns are raised regarding the integration of the PFIQ-7 instrument in our study, as its validation in the Greek female population included primarily women of older age, nearly half of whom were presented with symptoms of pelvic floor prolapse, which would not particularly pertain to our participants’ conditions.

**Conclusions**

Our study’s preliminary results revealed significant prevalence of sexual dysfunction in premenopausal women on endocrine therapy for breast cancer. More importantly, a possible association regarding type of treatment and effect on sexual functioning was detected, with aromatase inhibitors with concurrent ovarian function suppression displaying the greatest impact. Future research should investigate possible implication of confounding factors in these results. However, healthcare providers should be alert to sexual health problems, for early recognition and effective management.

**Acknowledgements**

I would like to express my deepest gratitude to all women who responded to our invitation and participated willingly in our study. My special thanks are extended to all contributors that assisted with the dissemination of our project to breast cancer survivors and especially the
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Αγγλόφωνο Πρόγραμμα Μεταπτυχιακών Σπουδών "Medical Research Methodology"

Διπλωματική Εργασία

Μελέτη σύγκρισης ταμοξιφαίνης και αναστολέων αρωματάσης στα πλαίσια επικουρικής θεραπείας σε προεμμηνοπαυσιακές γυναίκες με ορμονοευαίσθητο καρκίνο μαστού: Επιπλοκές από τη σεξουαλική σφαίρα και το αναπαραγωγικό σύστημα
Η έρευνα αυτή διεξάγεται στα πλαίσια εκπόνησης διπλωματικής εργασίας για την απόκτηση μεταπτυχιακού τίτλου στη «Μεθοδολογία της Ιατρικής Έρευνας» της Σχολής Επιστημών Υγείας, του τμήματος Ιατρικής, του Αριστοτελείου Πανεπιστημίου Θεσσαλονίκης. Σκοπός της διπλωματικής εργασίας είναι να διερευνήσει τις επιδράσεις της επικουρικής ορμονοθεραπείας στη σεξουαλική λειτουργία και το αναπαραγωγικό σύστημα σε προεμμηνοπαυσιακές γυναίκες με καρκίνο του μαστού.

Η θεραπεία με ταμοξιφαίνη ή αναστολείς αρωματάσης, με ή χωρίς καταστολή των ωοθηκών, έχει συσχετιστεί με πλήθος παρενέργειων από διάφορα όργανα και συστήματα του οργανισμού. Στην παρούσα μελέτη μελέτη θα εστιάσουμε στα προβλήματα γυναικολογικής και σεξουαλικής φύσεως που αντιμετωπίζουν οι γυναίκες που λαμβάνουν μακροχρόνια θεραπεία.

Η εμφάνιση συμπτωμάτων εμμηνόπαυσης (όπως εξάψεις, νευρικότητα, αϋπνία κτλ), η μείωση της σεξουαλικής δραστηριότητας και της libido, ο πόνος κατά τη σεξουαλική επαφή, και φυσικά η επίδραση στη γονιμότητα, αποτελούν μονάδες μόνο από τις πιθανές επιπλοκές, που οδηγούν σε μείωση του ιατρικού ποιοτικού ποιότητας και ενίσχυση σε προσωπική ή και οριστική διακοπή της θεραπείας. Συνεπώς, η σωστή ενημέρωση και η επίκοινη συνεργασία κάθε ασθενούς με τον ιατρό της για ανάλογα προβλήματα, είναι καθοριστικής σημασίας για την επιτυχία των θεραπευτικών στόχων και την εξασφάλιση μιας ομαλής καθημερινότητας.

Παρ’ όλα αυτά, οι επιδράσεις στη γυναικολογική και σεξουαλική υγεία της ασθενούς, συχνά περνούν αποκρατήρες από τους θεράποντες ιατρούς, μία έρευνα που εξετάζει τις προαναφερθείσες παρενέργειες κάθε φαρμάκου, μπορεί να προσφέρει όφελος στη βελτίωση και εξασφαλισμό μετοχικής διαχείρισης της ασθενούς με καρκίνο του μαστού, καθώς και στην προσωπική διαχείριση μετρών.

Η συμβολή σας στην επιτυχή διεξαγωγή της έρευνας είναι ιδιαίτερα σημαντική. Το ερωτηματολόγιό είναι ανώνυμο, εμπιστευτικό και τα αποτελέσματα θα χρησιμοποιηθούν αυστηρά και μόνο στα πλαίσια της στατιστικής ανάλυσης της έρευνας. Ο χρόνος που θα χρειαστείτε για την συμπλήρωση του ερωτηματολογίου είναι είκοσι με τριάντα λεπτά. 

Σας ευχαριστώ πολύ εκ των προτέρων για τη συμβολή και το χρόνο σας.
ΑΥΣΤΗΡΑ ΕΜΠΙΣΤΕΥΤΙΚΟ

Οδηγίες για την απάντηση των ερωτήσεων:

✓ Μην αναγράφετε το όνομά σας στο ερωτηματολόγιο
✓ Οι απαντήσεις που θα δώσετε θα κρατηθούν μυστικές
✓ Η συμμετοχή σας στην έρευνα είναι εθελοντική
✓ Σιγουρευτείτε ότι διαβάσατε προσεκτικά κάθε ερώτηση
✓ Τσεκάρετε ξεκάθαρα την επιλογή που προτιμάτε
✓ Απαντήστε βάζοντας X στο αντίστοιχο πλαίσιο
✓ Αν δε γνωρίζετε την απάντηση στις ερωτήσεις «ανοικτού τύπου» (χωρίς προκαθορισμένη απάντηση), σημειώστε «Δε γνωρίζω»

Παρακαλώ σημειώστε ότι δεν υπάρχουν «σωστές» ή «λανθασμένες» απαντήσεις· μας ενδιαφέρει η προσωπική σας εμπειρία και άποψη.
ΕΡΩΤΗΜΑΤΟΛΟΓΙΟ – ΠΡΩΤΟ ΜΕΡΟΣ

ΔΗΜΟΓΡΑΦΙΚΑ ΣΤΟΙΧΕΙΑ:

1) Ποια είναι η ημερομηνία γέννησής σας;

……………………………………………………………………………………………………………………………………………………………………

2) Ποια είναι η εθνικότητά σας; (όπως αναγράφεται στην ταυτότητα ή το διαβατήριό σας)

……………………………………………………………………………………………………………………………………………………………………

3) Ποια είναι η οικογενειακή σας κατάσταση;

□ Άγαμος/η
□ Έγγαμος/η
□ Διαζευγμένος/η
□ Χήρος/α
□ Άλλο (παρακαλώ συμπληρώστε)…………………………………………………………………………………………………………………

4) Έχετε παιδιά;

□ Ναι
□ Όχι
Αν απαντήσατε Ναι στην προηγούμενη ερώτηση, παρακαλώ αναφέρετε τον αριθμό των παιδιών σας και το φύλο.

5) Ποιο είναι το επίπεδο εκπαίδευσής σας;

□ Απόφοιτος Δημοτικού
□ Απόφοιτος Γυμνασίου
□ Απόφοιτος Λυκείου
□ Φοιτητής/Απόφοιτος Τεχνικής-Επαγγελματικής Σχολής (ΙΕΚ, ΟΑΕΔ, Ιδιωτ. Σχολές κτλ)
□ Φοιτητής/Απόφοιτος ΑΕΙ/ΤΕΙ
□ Κάτοχος μεταπτυχιακού/διδακτορικού διπλώματος
□ Άλλο (παρακαλώ συμπληρώστε).....................................................................................................................

6) Ποια είναι η επαγγελματική σας κατάσταση;

□ Δημόσιος Υπάλληλος
□ Ιδιωτικός Υπάλληλος
□ Ελεύθερος Επαγγελματίας
□ Συνταξιούχος/α
□ Άνεργος/η
□ Άλλο (παρακαλώ συμπληρώστε).....................................................................................................................
7) Αναγράψτε (αν γνωρίζετε) το στάδιο του καρκίνου κατά τη διάγνωση (π.χ. στάδιο 2A).

……………………………………………………………………………………………………………………………………………..

8) Ποιο ήταν το είδος του χειρουργείου σας;

□ Μαστεκτομή (αφαίρεση του ενός ή και των δύο μαστών)
□ Τμηματεκτομή/ογκεκτομή (αφαίρεση μόνο του όγκου-διατήρηση του στήθους)
□ Μαστεκτομή/τμηματεκτομή και λεμφαδενικός καθαρισμός (αφαίρεση λεμφαδένων από τη μασχάλη)
□ Μαστεκτομή και αποκατάσταση μαστών (πλαστική επέμβαση και «ανακατασκευή» του στήθους)
□ Δε γνωρίζω

9) Λάβατε χημειοθεραπεία;

□ Ναι
□ Όχι

10) Λάβατε ή λαμβάνετε βιολογικό παράγοντα Herceptin/Perjeta (δηλαδή υποδόρια ή ενδοφλέβια ένεση, κάθε 3 εβδομάδες, για ένα έτος) μετά το χειρουργείο; (αφορά τις HER2 θετικές γυναίκες)

□ Ναι
□ Όχι
□ Δε γνωρίζω
11) Λάβατε ακτινοθεραπεία (ακτινοβολία);

□ Ναι
□ Όχι

12) Είχατε περίοδο όταν διαγνωστήκατε με καρκίνο του μαστού;

□ Ναι
□ Όχι

Για τις γυναίκες >40 ετών:
Είχατε παρατηρήσει αλλαγές στην περίοδό σας το τελευταίο έτος πριν τη διάγνωση; (αύξηση μεσοδιαστημάτων εμμηνορρυσίας, αλλαγές στην ποσότητα του αίματος, ανώμαλος/ακανόνιστος εμμηνορρυσιακός κύκλος)

□ Ναι
□ Όχι

13) Λαμβάνετε ένεση για διακοπή της περιόδου;

□ Ναι
□ Όχι
□ Δε γνωρίζω

14) Αναγράψτε (αν γνωρίζετε) το όνομα του χαπιού ή της ουσίας που λαμβάνετε σαν ορμονοθεραπεία.
15) Πόσα χρόνια λαμβάνετε χάπι ορμονοθεραπείας για τον καρκίνο του μαστού; 
□ <3 μήνες  
□ >3 μήνες και <1 έτος  
□ 1-3 έτη  
□ >3 έτη 

16) Έχετε λάβει άλλο χάπι ορμονοθεραπείας εκτός από αυτό που λαμβάνετε τώρα; 
□ Ναι  
□ Όχι  
□ Δε γνωρίζω 

17) Έχετε στην οικογένειά σας (στενή και ευρύτερη) συγγενείς με καρκίνο του μαστού ή άλλο γυναικολογικό καρκίνο (π.χ. ωοθηκών, μήτρας, τραχήλου της μήτρας κτλ); 
□ Ναι  
□ Όχι  
□ Δε γνωρίζω 

18) Έχετε υποβληθεί ποτέ σε γονιδιακό έλεγχο για τον καρκίνο του μαστού; 
□ Ναι
Για όποιες απάντησαν Ναι στην προηγούμενη ερώτηση:

Έταν θετικό το αποτέλεσμα του γονιδιακού ελέγχου για κάποια μετάλλαξη;

□ Ναι
□ Όχι
□ Δε γνωρίζω

19) Παρακαλώ αναφέρετε άλλα προβλήματα υγείας που πιθανόν αντιμετωπίζετε (αφήστε κενό σε κάθε άλλη περίπτωση).

........................................................................................................................................................................

20) Παρακαλώ αναγράψτε, εφόσον γνωρίζετε, φάρμακα που τυχόν λαμβάνετε (π.χ. «λαμβάνω χάπια για πίεση, διαβήτη» κτλ). ΟΧΙ ΕΜΠΟΡΙΚΕΣ ΟΝΟΜΑΣΙΕΣ

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21) Λαμβάνετε κάποια αντικαταθλιπτική αγωγή;

□ Ναι
□ Όχι
□ Δε γνωρίζω
22) Καπνίζετε;

□ Ναι
□ Όχι

23) Ποιος ιατρός σας παρακολουθεί για τον καρκίνο του μαστού;

□ Χειρουργός Μαστού
□ Παθολόγος-Ογκολόγος
□ Γυναικολόγος
□ Άλλος……………………………………………………………………………………………

24) Έχετε επισκεφτεί γυναικολόγο το τελευταίο έτος;

□ Ναι
□ Όχι

25) Πόσο συχνά επισκέπτεστε ή επικοινωνείτε με το γυναικολόγο σας;

□ > 2 φορές το χρόνο
□ 1 φορά το εξάμηνο
□ 1 φορά το χρόνο
□ Σπάνια
□ Δεν έχω επισκεφτεί γυναικολόγο
26) Πόσο συχνά συζητάτε με τον ιατρό που σας παρακολουθεί ή το γυναικολόγο σας για προβλήματα σχετικά με τη σεξουαλική σας ζωή ή τη γυναικολογική σας υγεία;

□ Πολύ συχνά
□ Συχνά
□ Μερικές φορές
□ Σπάνια
□ Σχεδόν ποτέ ή ποτέ

27) Πόσο θεωρείτε ότι έχει επιδεινωθεί (έχει γίνει χειρότερη) στο σύνολό της η σεξουαλική σας ζωή μετά την έναρξη του χαπιού της ορμονοθεραπείας;

□ Πολύ
□ Αρκετά
□ Λίγο
□ Καθόλου

28) Σκέφτεστε να διακόψετε το χάπι της ορμονοθεραπείας λόγω επιδείνωσης της σεξουαλικής σας ζωής;

□ Πολύ συχνά
□ Συχνά
□ Μερικές φορές
□ Σπάνια
Ερωτήσεις σχετικά με την υγεία του γυναικείου αναπαραγωγικού συστήματος

Η κολπική ατροφία ή Ουρογεννητικό Σύνδρομο στην Εμμηνόπαυση είναι μια συχνή πάθηση που σχετίζεται με τη μείωση των οιστρογονικών επιπέδων και της δράσης τους στον κολπικό ιστό. Τα συμπτώματα περιλαμβάνουν ξηρότητα, ερεθισμό, πόνο και δυσπαρευνία (πόνο κατά τη σεξουαλική επαφή) μαζί με συχνουρία, έπειξη (ισχυρή και αιφνίδια επιθυμία) προς ούρηση και ακράτεια ούρων. Συνήθως αφορά γυναίκες κατά την εμμηνόπαυση. Ωστόσο, γυναίκες με καρκίνο του μαστού υποβάλλονται συχνά σε θεραπείες (ορμονοθεραπεία, χημειοθεραπεία κτλ) που προκαλούν ή επιδεινώνουν τα συμπτώματα.

Οι ακόλουθες ερωτήσεις έχουν σκοπό την εκτίμηση αυτών των επιπλοκών σε προεμμηνοπαυσιακές γυναίκες που λαμβάνουν επικουρική ορμονοθεραπεία για ορμονοευαίσθητο καρκίνο μαστού.

29) Ποια ομόσπονδος αντισφύλληψης ακολουθείτε; (Σημειώστε μία ή περισσότερες απαντήσεις)

□ Φυσικές μεθόδους (διακοπτόμενη συνουσία, πλύσεις ύστερα από την επαφή, αμηνόρροια του θηλασμού κτλ)

□ Αντρικό/γυναικείο προφυλακτικό

□ Αντισυλληπτικά δισκία

□ Ενδομήτρια σπειράματα

□ Σπερμακτόκτονα

□ Στειροποίηση (γυναικεία ή αντρική)
□ Επείγουσα αντισύλληψη (χάπι της «επόμενης μέρας»)

□ Αντισυλληπτικός σπόγγος

□ Καμία από τις παραπάνω

□ Άλλη......................................................................................................................................

30) Είχατε ποτέ κάποια αποβολή/διακοπή κύησης;

□ Ναι

□ Όχι

□ Δε γνωρίζω

31) Έχετε κάνει ποτέ έκτρωση;

□ Ναι

□ Όχι

32) Έχετε υποβληθεί σε καισαρική τομή;

□ Ναι

□ Όχι

33) Έχετε υποβληθεί σε αφαίρεση γεννητικών οργάνων (π.χ. ωοθηκών, σαλπίγγων, μήτρας κτλ.);

□ Ναι
Ìχι

Για τις γυναίκες που απάντησαν Ναι:

Αν γνωρίζετε, παρακαλώ αναγράψτε το όργανο ή όργανα που αφαιρέθηκαν.

…………………………………………………………………………………………………………………………………………………………

34) Είχατε διαγνωστεί πριν την έναρξη του χαπιού ορμονοθεραπείας με κάποια από τις
παρακάτω γυναικολογικές παθήσεις; (Σημειώστε μία ή περισσότερες απαντήσεις)

□ Ενδομητρίωση

□ Ινομύωμα μήτρας και τραχήλου

□ Πολύποδας/ες μήτρας και τραχήλου

□ Εξωμητρία κύηση

□ Ανατομικές ανωμαλίες μήτρας και τραχήλου (π.χ. σύνδρομο Asherman)

□ Μολύνσεις των γεννητικών οργάνων (μυκητίαση, κολπίτιδα, τραχηλίτιδα κτλ) ή της πυέλου
(περιοχή της λεκάνης)

□ Κονδυλώματα γεννητικών οργάνων

□ Λοίμωξη από τον ιό των ανθρωπίνων θηλυκάτων (HPV) ή άλλα σεξουαλικά μεταδιδόμενα
νοσήματα (χλαμύδια, έρπης, γονόρροια, τριχομονάδα κτλ)

□ Καμία από τις παραπάνω

□ Άλλη……………………………………………………………………………………………………………………………………

Από την έναρξη του χαπιού της ορμονοθεραπείας μέχρι σήμερα:
35) Έχετε διαγνωστεί με κάποια από τις παρακάτω γυναικολογικές παθήσεις; (Σημειώστε μία ή περισσότερες απαντήσεις)

☐ Ενδομητρίωση
☐ Ινομύωμα μήτρας και τραχήλου
☐ Πολύποδας/ες μήτρας και τραχήλου
☐ Εξωμήτρια κύηση
☐ Ανατομικές ανωμαλίες μήτρας και τραχήλου (π.χ. σύνδρομο Asherman)
☐ Μολύνσεις των γεννητικών οργάνων (μυκητίαση, κολπίτιδα, τραχηλίτιδα κτλ) ή της πυέλου (περιοχή της λεκάνης)
☐ Κονδυλώματα γεννητικών οργάνων
☐ Λοίμωξη από τον ιό των ανθρωπίνων θηλωμάτων (HPV) ή άλλα σεξουαλικώς μεταδιδόμενα νοσήματα (χλαμύδια, έρπης, γονόρροια, τριχομονάδα κτλ)
☐ Καμία από τις παραπάνω
☐ Άλλη………………………………………………………………………………………………………………………………………

36) Έχετε εφαρμόσει ποτέ ενυδατικές/λιπαντικές αλοιφές ή κρέμες για την τοπική θεραπεία της ξηρότητας του κόλπου;

☐ Ναι
☐ Όχι

37) Έχετε λάβει ποτέ κάποιο προϊόν για τα συμπτώματα της κολπικής ατροφίας (κολπικό δαικτύλιο, κολπικά δισκία ή κολπική κρέμα οιστρογόνων);
38) Έχετε υποβληθεί ποτέ σε γυναικολογικό υπέρηχο;
   □ Ναι
   □ Όχι
   □ Δε γνωρίζω

39) Κατά την τελευταία σας επίσκεψη στο γυναικολόγο, ήταν το πάχος του ενδομητρίου σας >5 mm (μεγαλύτερο από 5 χιλιοστά);
   □ Ναι
   □ Όχι
   □ Δε γνωρίζω

40) Έχετε υποβληθεί ή πρόκειται να υποβληθείτε σε απόξεση ενδομητρίου;
   □ Ναι
   □ Όχι
   □ Δε γνωρίζω

41) Έχετε διαγνωστεί με καρκίνο του ενδομητρίου;
42) Έχετε διαγνωστεί με άλλο γυναικολογικό καρκίνο (π.χ. ωοθηκών, τραχήλου της μήτρας κτλ.); □ Ναι □ Όχι □ Δε γνωρίζω

43) Έχετε παρατηρήσει αιμορραγία (ήπια απώλεια αίματος/σταγόνες αίματος) από τον κόλπο μετά τη σεξουαλική επαφή; □ Ναι □ Όχι □ Δε γνωρίζω □ Δεν επιδίωξα επαφή

Δυσπαρευνία ονομάζεται ο πόνος κατά τη διάρκεια της σεξουαλικής επαφής. Οι γυναίκες με δυσπαρευνία μπορεί να αισθάνονται επιφανειακό πόνο στην είσοδο του κόλπου, ή βαθύτερο πόνο κατά τη διάρκεια της διείσδυσης κατά την σεξουαλική επαφή.

44) Έχετε πόνο κατά τη διάρκεια ή μετά τη σεξουαλική επαφή (δυσπαρευνία);
□ Πολύ συχνά
□ Συχνά
□ Μερικές φορές
□ Σπάνια
□ Σχεδόν ποτέ ή ποτέ
□ Δεν επιδίωξα επαφή

45) Πόσο συχνά αισθάνεστε ξηρότητα στην περιοχή του κόλπου;
□ Πολύ συχνά
□ Συχνά
□ Μερικές φορές
□ Σπάνια
□ Σχεδόν ποτέ ή ποτέ

46) Πόσο συχνά αισθάνεστε κνησμό (φαγούρα) ή αίσθημα καύσου («κάψιμο») στην περιοχή του κόλπου;
□ Πολύ συχνά
□ Συχνά
□ Μερικές φορές
□ Σπάνια
□ Σχεδόν ποτέ ή ποτέ
47) Πόσο συχνά είναι η περιοχή του κόλπου σας ερεθισμένη (έντονα κόκκινη, με πόνο κτλ);

□ Πολύ συχνά
□ Συχνά
□ Μερικές φορές
□ Σπάνια
□ Σχεδόν ποτέ ή ποτέ

48) Έχετε παρατηρήσει αύξηση των εκκρίσεων του κόλπου σας;

□ Ναι
□ Όχι
□ Δε γνωρίζω

49) Έχετε παρατηρήσει δύσοσμες εκκρίσεις από τον κόλπο σας;

□ Ναι
□ Όχι
□ Δε γνωρίζω

50) Πόσο συχνά παθαίνετε μολύνσεις του ουροποιητικού και των γεννητικών οργάνων (ουρολοιμώξεις, κολπίτιδες, μυκητιάσεις κτλ);

□ Πολύ συχνά
□ Συχνά
□ Μερικές φορές
□ Σπάνια
□ Σχεδόν ποτέ ή ποτέ

**EORTC QLQ - BR23**

Oi ασθενείς αναφέρουν ορισμένες φορές ότι έχουν τα παρακάτω συμπτώματα ή προβλήματα.
Παρακαλούμε προσδιορίστε σε ποιο βαθμό είχατε αυτά τα συμπτώματα ή προβλήματα την προηγούμενη εβδομάδα.

<table>
<thead>
<tr>
<th>Κατά τη διάρκεια της τελευταίας εβδομάδας:</th>
<th>Καθόλου</th>
<th>Λίγο</th>
<th>Αρκετά</th>
<th>Πολύ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Το στόμα σας ήταν ξηρό;</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Τα τρόφιμα που καταναλώσατε είχαν διαφορετική γεύση απ’ ό,τι συνήθως;</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Τα μάτια σας πονούσαν, ήταν ερεθισμένα ή πιο υγρά;</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Είχατε τριχόπτωση;</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Απαντήστε σε αυτή την ερώτηση μόνον εάν είχατε τριχόπτωση:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H τριχόπτωση σας προκάλεσε ανησυχία;</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. Αισθανθήκατε άρρωστη ή αδιάθετη;</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Είχατε εξάψεις;</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Είχατε πονοκεφάλους;</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
9. Είχατε την αίσθηση ότι η εμφάνισή σας ήταν λιγότερο ελκυστική ως αποτέλεσμα της ασθένειας ή της θεραπείας σας;  
   1  2  3  4

10. Είχατε την αίσθηση ότι η θηλυκότητα σας έχει ελαττωθεί;  
    1  2  3  4

11. Δυσκολεύόσασταν να κοιτάξετε το σώμα σας γυμνό;  
    1  2  3  4

12. Αισθανόσασταν απογοήτευση με το σώμα σας;  
    1  2  3  4

13. Σας ανησυχούσε το θέμα της υγείας σας στο μέλλον;  
    1  2  3  4

Τις τέσσερις προηγούμενες εβδομάδες:  
Καθόλου Λίγο Αρκετά Πολύ

14. Πόσο σας ενδιέφερε το σεξ;  
    1  2  3  4

15. Σε ποιο βαθμό είχατε σεξουαλική δραστηριότητα (με ή χωρίς συνουσία);  
    1  2  3  4

16. Απαντήστε σε αυτή την ερώτηση μόνο εάν είχατε σεξουαλική δραστηριότητα: Πόσο απολαμβάνετε το σεξ;  
    1  2  3  4

Κατά τη διάρκεια της τελευταίας εβδομάδας:  
Καθόλου Λίγο Αρκετά Πολύ

17. Είχατε πόνο στο μπράτσο ή στον ώμο;  
    1  2  3  4

18. Το μπράτσο ή το χέρι σας ήταν πρησμένο;  
    1  2  3  4
19. Είχατε δυσκολία να σηκώσετε το μπράτσο σας ή να το κινήσετε προς το πλάι;  
1 2 3 4

20. Είχατε καθόλου πόνο στην περιοχή του προσβεβλημένου μαστού;  
1 2 3 4

21. Η περιοχή του προσβεβλημένου μαστού ήταν πρησμένη;  
1 2 3 4

22. Αισθανθήκατε υπερευαισθησία στην περιοχή του προσβεβλημένου μαστού;  
1 2 3 4

23. Είχατε δερματικά προβλήματα στην περιοχή του προσβεβλημένου μαστού (π.χ., φαγούρα, ξηροδερμία, ξεφλούδισμα);  
1 2 3 4

Female Sexual Function Index (FSFI)

Δείκτης Γυναικείας Σεξουαλικής Λειτουργίας

ΟΔΗΓΙΕΣ: Αυτές οι ερωτήσεις έχουν να κάνουν με τα σεξουαλικά συναισθήματα και αντιδράσεις σας κατά τη διάρκεια των τελευταίων 4 εβδομάδων. Παρακαλούμε απαντήστε τις ακόλουθες ερωτήσεις όσο το δυνατόν πιο ειλικρινά και ξεκάθαρα. Οι απαντήσεις σας θα κρατηθούν αποκλειστικά εμπιστευτικές. Για την απάντηση αυτών των ερωτήσεων, ισχύουν οι ακόλουθοι ορισμοί:

Η σεξουαλική δραστηριότητα μπορεί να περιλαμβάνει χάδια, προκαταρκτικά, αυνανισμό και κολπική συνουσία.

Η σεξουαλική συνουσία ορίζεται ως διείσδυση (είσοδος) του πέους στον κόλπο.

Ο σεξουαλικός ερεθισμός περιλαμβάνει καταστάσεις όπως τα προκαταρκτικά με σύντροφο,
αυτο-ερεθισμό (αυνανισμό), ή σεξουαλική φαντασίωση.

ΣΗΜΕΙΩΣΤΕ MONO ENA KOUTI ANA EΡΩΤΗΣΗ.

Η σεξουαλική επιθυμία ή ενδιαφέρον είναι ένα συναισθημα που περιλαμβάνει την επιθυμία να έχετε σεξουαλική εμπειρία, το αίσθημα της δεκτικότητας απέναντι στη σεξουαλική επιθυμία του συντρόφου σας και τη σκέψη ή φαντασίωση του να κάνετε σεξ.

1. Τις τελευταίες 4 εβδομάδες, πόσο συχνά νιώσατε σεξουαλική επιθυμία ή ενδιαφέρον;

   □ Σχεδόν συνέχεια ή συνέχεια

   □ Τις περισσότερες φορές (Περισσότερο από το μισό χρόνο)

   □ Αρκετές φορές (Περίπου το μισό χρόνο)

   □ Λίγες φορές (Λιγότερο από το μισό χρόνο)

   □ Σχεδόν ποτέ ή ποτέ

2. Τις τελευταίες 4 εβδομάδες, πώς θα βαθμολογούσατε το επίπεδο (βαθμό/ένταση) της σεξουαλικής σας επιθυμίας ή ενδιαφέροντος;

   □ Πολύ υψηλό

   □ Υψηλό

   □ Μέτριο

   □ Χαμηλό
Η σεξουαλική διέγερση είναι ένα συναίσθημα το οποίο περιλαμβάνει και σωματικές και νοητικές πτυχές του σεξουαλικού ερεθισμού. Μπορεί να περιλαμβάνει αισθήματα ζεστασιάς και γαργαλητού στα γεννητικά όργανα, εφύγρανση (υγρασία) ή μυϊκές συσπάσεις.

3. Τις τελευταίες 4 εβδομάδες, πόσο συχνά νιώσατε σεξουαλικά διεγερμένη («αναμμένη») κατά τη διάρκεια σεξουαλικής δραστηριότητας ή συνουσίας;

☐ Καμία σεξουαλική δραστηριότητα
☐ Σχεδόν πάντα ή πάντα
☐ Τις περισσότερες φορές (Περισσότερο από τις μισές φορές)
☐ Αρκετές φορές (Περίπου τις μισές φορές)
☐ Λίγες φορές (Λιγότερο από τις μισές φορές)
☐ Σχεδόν ποτέ ή ποτέ

4. Τις τελευταίες 4 εβδομάδες, πώς θα βαθμολογούσατε το επίπεδο της σεξουαλικής διέγερσής σας κατά τη διάρκεια της σεξουαλικής δραστηριότητας ή συνουσίας;

☐ Καμία σεξουαλική δραστηριότητα
☐ Πολύ υψηλό
☐ Υψηλό
☐ Μέτριο
☐ Χαμηλό
5. Τις τελευταίες 4 εβδομάδες, πόσο σίγουρη ήσασταν ότι θα διεγερθείτε σεξουαλικά κατά τη διάρκεια της σεξουαλικής δραστηριότητας ή συνουσίας;
□ Πολύ χαμηλό ή ανύπαρκτο
□ Καμία σεξουαλική δραστηριότητα
□ Πολύ μεγάλη σιγουριά
□ Μεγάλη σιγουριά
□ Μέτρια σιγουριά
□ Μικρή σιγουριά
□ Πολύ μικρή ή καθόλου σιγουριά

6. Τις τελευταίες 4 εβδομάδες, πόσο συχνά νιώσατε ικανοποιημένη από τη διέγερση (έξαψη) σας κατά τη διάρκεια σεξουαλικής δραστηριότητας ή συνουσίας;
□ Καμία σεξουαλική δραστηριότητα
□ Σχεδόν πάντα ή πάντα
□ Τις περισσότερες φορές (Περισσότερο από τις μισές φορές)
□ Αρκετές φορές (Περίπου τις μισές φορές)
□ Λίγες φορές (Λιγότερο από τις μισές φορές)
□ Σχεδόν ποτέ ή ποτέ

7. Τις τελευταίες 4 εβδομάδες, πόσο συχνά εφυγρανθήκατε (γίνατε «υγρή») κατά τη διάρκεια σεξουαλικής δραστηριότητας ή συνουσίας;
□ Καμία σεξουαλική δραστηριότητα
□ Σχεδόν πάντα ή πάντα
□ Τις περισσότερες φορές (Περισσότερο από τις μισές φορές)
□ Αρκετές φορές (Περίπου τις μισές φορές)
□ Λίγες φορές (Λιγότερο από τις μισές φορές)
□ Σχεδόν ποτέ ή ποτέ

8. Τις τελευταίες 4 εβδομάδες, πόσο δύσκολο ήταν να εφυγρανθείτε (να γίνετε «υγρή») κατά τη διάρκεια σεξουαλικής δραστηριότητας ή συνουσίας;
□ Καμία σεξουαλική δραστηριότητα
□ Εξαιρετικά δύσκολο ή αδύνατο
□ Πολύ δύσκολο
□ Δύσκολο
□ Ελαφρά δύσκολο
□ Όχι δύσκολο

9. Τις τελευταίες 4 εβδομάδες, πόσο συχνά διατηρήσατε την εφύγρανσή σας («υγρότητα») μέχρι το τέλος της σεξουαλικής δραστηριότητας ή συνουσίας;
□ Καμία σεξουαλική δραστηριότητα
□ Σχεδόν πάντα ή πάντα
□ Τις περισσότερες φορές (Περισσότερο από τις μισές φορές)
10. Τις τελευταίες 4 εβδομάδες, πόσο δύσκολο ήταν να διατηρήσετε την εφύγρανσή σας («υγρότητα») μέχρι το τέλος της σεξουαλικής δραστηριότητας ή συνουσίας;

□ Καμία σεξουαλική δραστηριότητα
□ Εξαιρετικά δύσκολο ή αδύνατο
□ Πολύ δύσκολο
□ Δύσκολο
□ Ελαφρά δύσκολο
□ Όχι δύσκολο

11. Τις τελευταίες 4 εβδομάδες, όταν είχατε σεξουαλικό ερεθισμό ή συνουσία πόσο συχνά φθάνατε σε οργασμό (κορύφωση);

□ Καμία σεξουαλική δραστηριότητα
□ Σχεδόν πάντα ή πάντα
□ Τις περισσότερες φορές (Περισσότερο από τις μισές φορές)
□ Αρκετές φορές (Περίπου τις μισές φορές)
□ Λίγες φορές (Λιγότερο από τις μισές φορές)
□ Σχεδόν ποτέ ή ποτέ
12. Τις τελευταίες 4 εβδομάδες, όταν είχατε σεξουαλικό ερεθισμό ή συνουσία πόσο δύσκολο ήταν για εσάς να φθάσετε σε οργασμό (κορύφωση);

□ Καμία σεξουαλική δραστηριότητα
□ Εξαιρετικά δύσκολο ή αδύνατο
□ Πολύ δύσκολο
□ Δύσκολο
□ Ελαφρά δύσκολο
□ Όχι δύσκολο

13. Τις τελευταίες 4 εβδομάδες, πόσο ικανοποιημένη είστε με την ικανότητά σας να φθάσετε σε οργασμό (κορύφωση);

□ Καμία σεξουαλική δραστηριότητα
□ Πολύ ικανοποιημένη
□ Μετρίως ικανοποιημένη
□ Σχεδόν το ίδιο ικανοποιημένη και δυσαρεστημένη
□ Μετρίως δυσαρεστημένη
□ Πολύ δυσαρεστημένη

14. Τις τελευταίες 4 εβδομάδες, πόσο ικανοποιημένη είστε με τη συναισθηματική εγγύτητα κατά τη σεξουαλική δραστηριότητα μεταξύ εσάς και του συντρόφου σας;

□ Δεν έχω ερωτικό σύντροφο
□ Καμία σεξουαλική δραστηριότητα
15. Τις τελευταίες 4 εβδομάδες, πόσο ικανοποιημένη είστε με τη σεξουαλική σας σχέση με το σύντροφό σας;

□ Δεν έχω ερωτικό σύντροφο
□ Πολύ ικανοποιημένη
□ Μετρίως ικανοποιημένη
□ Σχεδόν το ίδιο ικανοποιημένη και δυσαρεστημένη
□ Μετρίως δυσαρεστημένη
□ Πολύ δυσαρεστημένη

16. Τις τελευταίες 4 εβδομάδες, πόσο ικανοποιημένη είστε με τη συνολική σεξουαλική σας ζωή;

□ Πολύ ικανοποιημένη
□ Μετρίως ικανοποιημένη
□ Σχεδόν το ίδιο ικανοποιημένη και δυσαρεστημένη
□ Μετρίως δυσαρεστημένη
17. Τις τελευταίες 4 εβδομάδες, πόσο συχνά νιώσατε ενόχληση ή πόνο κατά τη διάρκεια κολπικής διείσδυσης:

☐ Πολύ δυσαρεστημένη

☐ Δεν επιχείρησα συνουσία

☐ Σχεδόν πάντα ή πάντα

☐ Τις περισσότερες φορές (Περισσότερο από τις μισές φορές)

☐ Αρκετές φορές (Περίπου τις μισές φορές)

☐ Λίγες φορές (Λιγότερο από τις μισές φορές)

☐ Σχεδόν ποτέ ή ποτέ

18. Τις τελευταίες 4 εβδομάδες, πόσο συχνά νιώσατε ενόχληση ή πόνο μετά την κολπική διείσδυση:

☐ Δεν επιχείρησα συνουσία

☐ Σχεδόν πάντα ή πάντα

☐ Τις περισσότερες φορές (Περισσότερο από τις μισές φορές)

☐ Αρκετές φορές (Περίπου τις μισές φορές)

☐ Λίγες φορές (Λιγότερο από τις μισές φορές)

☐ Σχεδόν ποτέ ή ποτέ

19. Τις τελευταίες 4 εβδομάδες, πώς θα βαθμολογούσατε το επίπεδο (βαθμό) ενόχλησης ή πόνου κατά τη διάρκεια ή μετά τη κολπική διείσδυση;

☐ Δεν επιχείρησα συνουσία
Ερωτηματολόγιο Καταγραφής Δυσφορίας της Ακράτειας Ούρων (UDI-6)

Οι ερωτήσεις αυτές θα σας ζητήσουν να περιγράψετε αν έχετε κάποια συμπτώματα από την ουροδόχο κύστη ή την πύελο και αν έχετε, σε ποιο βαθμό σας ενοχλούν. Κατά τη συμπλήρωση των ερωτήσεων σας παρακαλούμε να υπολογίζετε τα συμπτώματά σας κατά τη διάρκεια των τελευταίων 3 μηνών.

1) Έχετε συνήθως συχνουρία;

☐ Όχι ☐ Ναι. Πόσο σας ενοχλεί αυτό; ☐ Καθόλου

☐ Λίγο ☐ Μέτρια ☐ Πολύ

2) Σας τυχαίνει συνήθως να χάνετε ούρα (να λερώνεστε) όταν νιώθετε επείγουσα ή έντονη επιθυμία να ουρήσετε;

☐ Όχι ☐ Ναι. Πόσο σας ενοχλεί αυτό; ☐ Καθόλου

☐ Λίγο ☐ Μέτρια
3) Χάνετε ούρα (λερώνεστε) συνήθως με το βήχα, το φτέρνισμα ή το γέλιο;

☐ Όχι ☐ Ναι. Πόσο σας ενοχλεί αυτό; ☐ Καθόλου
☐ Λίγο
☐ Μέτρια
☐ Πολύ

4) Χάνετε συνήθως (λερώνεστε με) σταγόνες ούρων;

☐ Όχι ☐ Ναι. Πόσο σας ενοχλεί αυτό; ☐ Καθόλου
☐ Λίγο
☐ Μέτρια
☐ Πολύ

5) Δυσκολεύεστε συνήθως να ουρήσετε;

☐ Όχι ☐ Ναι. Πόσο σας ενοχλεί αυτό; ☐ Καθόλου
☐ Λίγο
☐ Μέτρια
☐ Πολύ

6) Αισθάνεστε συνήθως πόνο ή ενόχληση χαμηλά στην κοιλιά ή στα γεννητικά όργανα;
Ερωτηματολόγιο για τις Επιπτώσεις των Διαταραχών του Πυελικού Εδάφους (PFIQ-7)

Κάποιες γυναίκες βρίσκουν ότι τα συμπτώματα που έχουν από την ουροδόχο κύστη ή τον κόλπο, επηρεάζουν τις καθημερινές τους δραστηριότητες, τις σχέσεις τους και τα συναισθήματά τους. Για κάθε ερώτηση τοποθετήστε X στην απάντηση που περιγράφει καλύτερα πόσο πολύ/σε ποιο βαθμό έχουν επηρεαστεί οι δραστηριότητες, οι διαπροσωπικές σας σχέσεις, ή τα συναισθήματα σας, από συμπτώματα ή καταστάσεις που σχετίζονται με την ουροδόχο κύστη ή τον κόλπο σας στο διάστημα των τελευταίων 3 μηνών.

(PFIQ-7/UIQ-7)

Πόσο τα συμπτώματα ή τα προβλήματα που έχετε με την ουροδόχο κύστη ή την ούρηση επηρεάζουν:

1) τις δουλειές σας για το σπίτι (π.χ. μαγείρεμα, νοικοκυριό);
   - Όχι
   - Ναι
   - Καθόλου
   - Λίγο
   - Μέτρια
   - Πολύ

2) τις σωματικές σας δραστηριότητες (π.χ. περπάτημα, κολύμβηση, γυμναστική);
   - Όχι
   - Ναι
   - Καθόλου
   - Λίγο
   - Μέτρια
   - Πολύ

3) την ψυχαγωγία σας (π.χ. να πάτε σινεμά ή σε μία συναυλία);
   - Όχι
   - Ναι
   - Καθόλου
   - Λίγο
   - Μέτρια
   - Πολύ
4) τη δυνατότητά σας να ταξιδεύετε για πάνω από μισή ώρα με το λεωφορείο ή το αυτοκίνητο;
 □ Καθόλου □ Λίγο □ Μέτρια □ Πολύ

5) τις εκτός σπιτιού κοινωνικές σας δραστηριότητες;
 □ Καθόλου □ Λίγο □ Μέτρια □ Πολύ

6) τη συναισθηματική σας κατάσταση (π.χ. νευρικότητα, κατάθλιψη κτλ.);
 □ Καθόλου □ Λίγο □ Μέτρια □ Πολύ

7) Αισθάνεστε απογοήτευση ή νιώθετε άβολα;
 □ Καθόλου □ Λίγο □ Μέτρια □ Πολύ

(PFIQ-7/UIQ-7)

Πόσο τα συμπτώματα ή τα προβλήματα που έχετε με τον κόλπο ή την πύελο (λεκάνη) επηρεάζουν:

1) τις δουλειές σας για το σπίτι (π.χ. μαγείρεμα, νοικοκυριό);
 □ Καθόλου □ Λίγο □ Μέτρια □ Πολύ

2) τις σωματικές σας δραστηριότητες (π.χ. περπάτημα, κολύμβηση, γυμναστική);
 □ Καθόλου □ Λίγο □ Μέτρια □ Πολύ

3) την ψυχαγωγία σας (π.χ. να πάτε σινεμά ή σε μία συναυλία);
 □ Καθόλου □ Λίγο □ Μέτρια □ Πολύ

4) τη δυνατότητά σας να ταξιδεύετε για πάνω από μισή ώρα με το λεωφορείο ή το αυτοκίνητο;
 □ Καθόλου □ Λίγο □ Μέτρια □ Πολύ
5) τις εκτός σπιτιού κοινωνικές σας δραστηριότητες;

☐ Καθόλου ☐ Λίγο ☐ Μέτρια ☐ Πολύ

6) τη συναισθηματική σας κατάσταση (π.χ. νευρικότητα, κατάθλιψη κτλ);

☐ Καθόλου ☐ Λίγο ☐ Μέτρια ☐ Πολύ

7) Αισθάνεστε απογοήτευση ή νιώθετε άβολα;

☐ Καθόλου ☐ Λίγο ☐ Μέτρια ☐ Πολύ

Ευχαριστούμε που συμπληρώσατε αυτό το ερωτηματολόγιο!
Tamoxifen versus aromatase inhibitors as adjuvant therapy in premenopausal women with hormone receptor-positive breast cancer; effects on sexuality and the female reproductive system
The present research is carried out as part of a master’s thesis in “Methodology of Medical Research” of the School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki. The aim of this study is to investigate the effects of adjuvant hormone therapy on sexual function and the female reproductive system in premenopausal women with breast cancer.

Treatment with tamoxifen or aromatase inhibitors, with or without ovarian function suppression, has been associated with multiple side effects from various organs and systems of the body. In this study we will focus on the gynecological and sexual problems faced by women receiving long-term treatment. Menopause symptoms (such as hot flashes, nervousness, insomnia, etc.), decreased sexual activity and libido, pain during sexual intercourse, and of course reproductive and fertility disorders, are just some of the possible complications, leading to deterioration in quality of life and often temporary or even permanent discontinuation of treatment. Therefore, effective patient-physician communication, comprehensive information on what to expect and how to handle it, as well as proper education are crucial to the therapeutic process and help ensure a smooth daily routine for the patient.

Nevertheless, the impact on the patient's gynecological and sexual health often goes unnoticed by doctors. For this reason, a study examining the aforementioned side effects of each drug may prove beneficial to the individualized management of breast cancer patients as well as the promotion of preventive measures.

Your contribution to the successful conduct of this research is particularly important. The questionnaire is anonymous, confidential and the results will be used strictly and only in the context of the statistical analysis of the survey. The time you will need to complete the questionnaire is twenty to thirty minutes.

Thank you in advance for your time and contribution.
Instructions for answering questions:

➢ Do not include your name in the questionnaire
➢ The answers you give will be kept secret
➢ Your participation in the survey is voluntary
➢ Make sure you read carefully each question
➢ Check the answer in the corresponding box
➢ If you do not know the answer to "open-ended" questions (no predefined answer), please note "Do not know"

Please note that there are no "correct" or "wrong" answers; we are interested in your personal experience and opinion.
QUESTIONNAIRE – PART ONE

Demographics:

1) What is your date of birth?

............................................................................................................................................................

2) What is your nationality?

............................................................................................................................................................

3) What is your marital status?

☐ Single

☐ Married

☐ Divorced

☐ Widowed

☐ Other (please specify)................................................................................................................................

4) Do you have any children?

☐ Yes

☐ No
If you answered Yes to the previous question, please write down the number and gender of your children.

5) What is your level of education?

☐ Primary Education

☐ Lower Secondary Education

☐ Upper Secondary Education

☐ Vocational Education and Training

☐ Bachelor or equivalent

☐ Master/doctoral or equivalent

☐ Other (please specify)..........................................................................................................................................................

6) What is your employment status?

☐ Public Sector Employee

☐ Private Sector Employee

☐ Self-employed

☐ Retired

☐ Unemployed

☐ Other (please specify).............................................................................................................................................................
7) Select (if you know) the stage of your breast cancer upon diagnosis (eg Stage 2A).


8) What was your type of surgery?

  □ Mastectomy (removal of one or both breasts)
  □ Breast-conserving surgery (removal of the breast tumor/lumpectomy)
  □ Mastectomy/breast-conserving surgery and axillary lymph node dissection
  □ Mastectomy and breast reconstruction
  □ I don’t know

9) Did you receive chemotherapy treatment?

  □ Yes
  □ No

10) Did you receive or currently receiving a targeted biological agent (ie subcutaneous or intravenous injection every 3 weeks for one year) after surgery? (for HER2 positive women)

  □ Yes
  □ No
  □ I don’t know

11) Did you receive radiation therapy?
12) Did you have period (menstrual cycle) when first diagnosed with breast cancer?
   □ Yes
   □ No

For women > 40 years old:

Did you notice changes in your period the year before diagnosis? (increase in menstrual cycle length, changes in blood volume, abnormal / irregular menstrual cycle)
   □ Yes
   □ No

13) Do you receive an injection that stops menstruation (stops you from getting your period)?
   □ Yes
   □ No
   □ I don’t know

14) Write down (if you know) the name of the drug or active ingredient you are taking as hormone therapy.

............................................................................................................................................................................
15) How many years have you been taking hormone therapy for breast cancer?

☐ <3 months
☐ >3 months and <1 year
☐ 1-3 years
☐ >3 years

16) Have you taken any other drug as hormone therapy besides what you are receiving now?

☐ Yes
☐ No
☐ I don’t know

17) Do you have any relatives with breast or other gynaecological cancers (eg ovarian, uterine, cervical, etc.)?

☐ Yes
☐ No
☐ I don’t know

18) Have you ever undergone genetic testing for breast cancer?

☐ Yes
☐ No
For those who answered Yes to the previous question:

Was the result of the gene testing positive for a mutation?

☐ Yes

☐ No

☐ I don’t know

19) Please report any other health problems you may be experiencing (leave blank in any other case).

………………………………………………………………………………………………………………………………………………………………

20) Please write down, if you know, any medications you may be taking (eg "I take medication for high blood pressure, diabetes, hypothyroidism" etc.). NO TRADE NAMES

………………………………………………………………………………………………………………………………………………………………

21) Are you taking any antidepressant treatment?

☐ Yes

☐ No

☐ I don’t know
22) Are you a smoker?

☐ Yes

☐ No

23) Which doctor is responsible for your follow-up care for breast cancer?

☐ Breast Surgeon

☐ Medical Oncologist

☐ Gynecologist

☐ Other (please specify)…………………………………………………………………………………………………………………………………………………………………………………………

24) Have you visited your gynaecologist in the last year?

☐ Yes

☐ No

25) How often do you visit or contact your gynaecologist?

☐ > 2 times a year

☐ once every six months

☐ once a year

☐ Rarely

☐ I have never visited a gynecologist
26) How often do you discuss with your doctor or your gynaecologist about issues related to your sexual or gynecological health?

- Very frequently
- Frequently
- Occasionally
- Rarely
- Very rarely or never

27) How much do you think your sexual life has become worse after the onset of the hormone therapy?

- Extremely
- Very
- Slightly
- Not at all

28) Do you ever consider stopping the hormone therapy because it worsens your sex life?

- Very frequently
- Frequently
- Occasionally
- Rarely
- Very rarely or never
QUESTONNAIRE – PART TWO

Questions regarding the health of the female reproductive system

Vaginal atrophy or Urogenital Syndrome in Menopause is a common condition associated with the reduction of estrogenic levels and their action on vaginal tissue. Symptoms include dryness, irritation, pain and dyspareunia (pain during sexual intercourse) along with increased frequency, urge (strong and sudden desire) to urinate and urinary incontinence. It usually affects women during menopause. However, women with breast cancer often undergo treatments (hormone therapy, chemotherapy etc.) that cause or exacerbate the symptoms.

The following questions are intended to evaluate these complications in premenopausal women receiving adjuvant hormone therapy for hormonereceptor- positive breast cancer.

29) Which method of contraception do you use? (Please select one or more answers)

- Physical methods (natural family planning, withdrawal method, washing the inner and outer female genitals, lactational amenorrhea method, etc.)
- Male/Female condom
- Oral contraceptives (birth control pills)
- Intrauterine devices/systems
- Spermicides
- Sterilization (male/female)
- Emergency contraception ("morning-after" pill)
- Contraceptive sponge
- None of the above
30) Have you ever had a miscarriage?

- Yes
- No
- I don’t know

31) Have you ever had an abortion?

- Yes
- No

32) Have you ever had a cesarean section (C-section)?

- Yes
- No

33) Have you removed surgically any of your reproductive organs (e.g. ovaries, fallopian tubes, uterus, etc.)?

- Yes
- No

For women who answered Yes:
If you know, please write down the organ removed.

……………………………………………………………………………………………………………………………………..

34) Had you ever been diagnosed with any of the following gynecological conditions, before the onset of the hormone therapy? (Please select one or more answers)

□ Endometriosis

□ Uterine/cervical fibroids

□ Uterine/cervical polyps

□ Ectopic pregnancy

□ Congenital or acquired uterine and cervical disorders (e.g. Asherman's syndrome)

□ Genital tract infections (fungal infections, vaginal/ cervical infections, etc.) or pelvic infections

□ Genital warts

□ Human papillomavirus (HPV) infection or other sexually transmitted diseases (chlamydia, genital herpes, gonorrhea, trichomoniasis etc.)

□ None of the above

□ Other (please specify)

……………………………………………………………………………………………………………………………………..

From the beginning of the hormone therapy to date;
35) Have you ever been diagnosed with any of the following gynaecological conditions? (Please select one or more answers)

- □ Endometriosis
- □ Uterine/cervical fibroids
- □ Uterine/cervical polyps
- □ Ectopic pregnancy
- □ Congenital or acquired uterine and cervical disorders (e.g. Asherman's syndrome)
- □ Genital tract infections (fungal infections, vaginal/ cervical infections, etc.) or pelvic infections
- □ Genital warts
- □ Human papillomavirus (HPV) infection or other sexually transmitted diseases (chlamydia, genital herpes, gonorrhea, trichomoniasis etc.)
- □ None of the above
- □ Other (please specify)

……………………………………………………………………………………………………………………………………….

36) Have you ever applied moisturizing/lubricating ointments or creams for the topical treatment of vaginal dryness?

- □ Yes
- □ No

37) Have you ever used a product for the symptoms of vaginal atrophy (estradiol vaginal...
ring/tablets/cream)?

☐ Yes

☐ No

☐ I don’t know

38) Have you ever had a transvaginal or pelvic ultrasound?

☐ Yes

☐ No

☐ I don’t know

39) On your last visit to the gynecologist, was the endometrial thickness > 5 mm (greater than 5 mm)?

☐ Yes

☐ No

☐ I don’t know

40) Have you ever had or going to have endometrial ablation (removal of the uterine lining)?

☐ Yes

☐ No

☐ I don’t know
41) Have you ever been diagnosed with endometrial cancer?

☐ Yes

☐ No

☐ I don’t know

42) Have you ever been diagnosed with other gynecological cancers (e.g. ovarian, cervical etc.)?

☐ Yes

☐ No

☐ I don’t know

43) Have you ever experienced vaginal bleeding (mild blood loss or drops of blood) after sexual intercourse?

☐ Yes

☐ No

☐ I don’t know

☐ I didn’t attempt sexual intercourse

Dyspareunia is pain during sexual intercourse. Women with dyspareunia may feel superficial pain at the entrance of the vagina, or deeper pain during penetration.
44) Do you have pain during or after sexual intercourse (dyspareunia)?

- Very frequently
- Frequently
- Occasionally
- Rarely
- Very rarely or never
- I didn’t attempt sexual intercourse

45) How often do you feel vaginal dryness?

- Very frequently
- Frequently
- Occasionally
- Rarely
- Very rarely or never

46) How often do you experience pruritus (itching) or burning sensation in your vagina?

- Very frequently
- Frequently
- Occasionally
- Rarely
- Very rarely or never
47) How often do you feel your vagina and vulva irritated (skin redness, pain etc)?

☐ Very frequently

☐ Frequently

☐ Occasionally

☐ Rarely

☐ Very rarely or never

48) Have you noticed an increase in your vaginal discharge?

☐ Yes

☐ No

☐ I don’t know

49) Have you noticed vaginal secretions with an unpleasant odor?

☐ Yes

☐ No

☐ I don’t know

50) How often do you get urinary and genital tract infections (vaginitis, fungal infections, etc.)?

☐ Very frequently
□ Frequently

□ Occasionally

□ Rarely

□ Very rarely or never

**EORTC QLQ - BR23**

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

<table>
<thead>
<tr>
<th>During the past week:</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Did you have a dry mouth?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Did food and drink taste different than usual?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Were your eyes painful, irritated or watery?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Have you lost any hair?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Answer this question only if you had any hair loss:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were you upset by the loss of your hair?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. Did you feel ill or unwell?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Did you have hot flushes?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Did you have headaches?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. Have you felt physically less attractive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
10. Have you been feeling less feminine as a result of your disease or treatment? 1 2 3 4
11. Did you find it difficult to look at yourself naked? 1 2 3 4
12. Have you been dissatisfied with your body? 1 2 3 4
13. Were you worried about your health in the future? 1 2 3 4

### During the past four weeks:

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>14. To what extent were you interested in sex?</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. To what extent were you sexually active? (with or without intercourse)</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### During the past week:

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Did you have any pain in your arm or shoulder?</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. Did you have a swollen arm or hand?</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. Was it difficult to raise your arm or to move it sideways?</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 20. Have you had any pain in the area of your
affected breast? 1 2 3 4

21. Was the area of your affected breast swollen? 1 2 3 4

22. Was the area of your affected breast oversensitive? 1 2 3 4

23. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)? 1 2 3 4

Female Sexual Function Index (FSFI)

INSTRUCTIONS: These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation and vaginal intercourse.

Sexual intercourse is defined as penile penetration (entry) of the vagina.

Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CHECK ONLY ONE BOX PER QUESTION.

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how often did you feel sexual desire or interest?

□ Almost always or always
2. Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?

- Very high
- High
- Moderate
- Low
- Very low or none at all

Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how often did you feel sexually aroused ("turned on") during sexual activity or intercourse?

- No sexual activity
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
4. Over the past 4 weeks, how would you rate your level of sexual arousal ("turn on") during sexual activity or intercourse?

- No sexual activity
- Very high
- High
- Moderate
- Low
- Very low or none at all

5. Over the past 4 weeks, how confident were you about becoming sexually aroused during sexual activity or intercourse?

- No sexual activity
- Very high confidence
- High confidence
- Moderate confidence
- Low confidence
- Very low or no confidence
6. Over the past 4 weeks, how often have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

□ No sexual activity
□ Almost always or always
□ Most times (more than half the time)
□ Sometimes (about half the time)
□ A few times (less than half the time)
□ Almost never or never

7. Over the past 4 weeks, how often did you become lubricated ("wet") during sexual activity or intercourse?

□ No sexual activity
□ Almost always or always
□ Most times (more than half the time)
□ Sometimes (about half the time)
□ A few times (less than half the time)
□ Almost never or never

8. Over the past 4 weeks, how difficult was it to become lubricated ("wet") during sexual activity or intercourse?

□ No sexual activity
□ Extremely difficult or impossible
9. Over the past 4 weeks, how often did you maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

- No sexual activity
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

10. Over the past 4 weeks, how difficult was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

- No sexual activity
- Extremely difficult or impossible
- Very difficult
- Difficult
- Slightly difficult
11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how often did you reach orgasm (climax)?

☐ No sexual activity

☐ Almost always or always

☐ Most times (more than half the time)

☐ Sometimes (about half the time)

☐ A few times (less than half the time)

☐ Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how difficult was it for you to reach orgasm (climax)?

☐ No sexual activity

☐ Extremely difficult or impossible

☐ Very difficult

☐ Difficult

☐ Slightly difficult

☐ Not difficult

13. Over the past 4 weeks, how satisfied were you with your ability to reach orgasm (climax) during sexual activity or intercourse?
14. Over the past 4 weeks, how satisfied have you been with the amount of emotional closeness during sexual activity between you and your partner?

- No sexual partner
- No sexual activity
- Very satisfied
- Moderately satisfied
- About equally satisfied and dissatisfied
- Moderately dissatisfied
- Very dissatisfied

15. Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?

- No sexual partner
- Very satisfied
□ Moderately satisfied
□ About equally satisfied and dissatisfied
□ Moderately dissatisfied
□ Very dissatisfied

16. Over the past 4 weeks, how satisfied have you been with your overall sexual life?
□ Very satisfied
□ Moderately satisfied
□ About equally satisfied and dissatisfied
□ Moderately dissatisfied
□ Very dissatisfied

17. Over the past 4 weeks, how often did you experience discomfort or pain during vaginal penetration?
□ Did not attempt intercourse
□ Almost always or always
□ Most times (more than half the time)
□ Sometimes (about half the time)
□ A few times (less than half the time)
□ Almost never or never
18. Over the past 4 weeks, how often did you experience discomfort or pain following vaginal penetration?

☐ Did not attempt intercourse

☐ Almost always or always

☐ Most times (more than half the time)

☐ Sometimes (about half the time)

☐ A few times (less than half the time)

☐ Almost never or never

19. Over the past 4 weeks, how would you rate your level (degree) of discomfort or pain during or following vaginal penetration?

☐ Did not attempt intercourse

☐ Very high

☐ High

☐ Moderate

☐ Low

☐ Very low or none at all

Urogenital Distress Inventory (UDI-6)

While answering these questions, please consider your symptoms over the last three months. We realize that you may not be having problems in some of these areas, but please answer these questions as completely as possible.
Do you...

1) Usually experience frequent urination?
   □ No □ Yes. How much does it bother you? □ Not at all
   □ A little bit □ Moderately □ Greatly

2) Usually experience urine leakage associated with a feeling of urgency, that is, a strong sensation of needing to go to the bathroom?
   □ No □ Yes. How much does it bother you? □ Not at all
   □ A little bit □ Moderately □ Greatly

3) Usually experience urine leakage related to coughing, sneezing or laughing?
   □ No □ Yes. How much does it bother you? □ Not at all
   □ A little bit □ Moderately □ Greatly

4) Usually experience small amounts of urine leakage (that is, drops)?
   □ No □ Yes. How much does it bother you? □ Not at all
5) Usually experience difficulty emptying your bladder?

□ No  □ Yes. How much does it bother you?  □ Not at all
□ A little bit  □ Moderately  □ Greatly

6) Usually experience pain or discomfort in the lower abdomen or genital region?

□ No  □ Yes. How much does it bother you?  □ Not at all
□ A little bit  □ Moderately  □ Greatly

Pelvic Floor Impact Questionnaire (PFIQ-7)

Some women find that bladder or vaginal symptoms affect their activities, relationships, and feelings. For each question select the response that best describes how much your activities, relationships, or feelings have been affected by your bladder or vaginal symptoms or conditions over the last 3 months.
How do symptoms or conditions in your bladder or urine usually affect your...

1) Ability to do household chores (cooking, laundry, housecleaning)?
   □ Not at all  □ Somewhat □ Moderately □ Quite a bit

2) Ability to do physical activities such as walking, swimming, or other exercise?
   □ Not at all  □ Somewhat □ Moderately □ Quite a bit

3) Entertainment activities such as going to a movie or concert?
   □ Not at all  □ Somewhat □ Moderately □ Quite a bit

4) Ability to travel by car or bus for a distance greater than 30 minutes away from home?
   □ Not at all  □ Somewhat □ Moderately □ Quite a bit

5) Participating in social activities outside your home?
   □ Not at all  □ Somewhat □ Moderately □ Quite a bit

6) Emotional health (nervousness, depression, etc)?
   □ Not at all  □ Somewhat □ Moderately □ Quite a bit

7) Feeling frustrated?
   □ Not at all  □ Somewhat □ Moderately □ Quite a bit

How do symptoms or conditions in your vagina or pelvis usually affect your...

1) Ability to do household chores (cooking, laundry, housecleaning)?
   □ Not at all  □ Somewhat □ Moderately □ Quite a bit
2) Ability to do physical activities such as walking, swimming, or other exercise?

☐ Not at all  ☐ Somewhat  ☐ Moderately  ☐ Quite a bit

3) Entertainment activities such as going to a movie or concert?

☐ Not at all  ☐ Somewhat  ☐ Moderately  ☐ Quite a bit

4) Ability to travel by car or bus for a distance greater than 30 minutes away from home?

☐ Not at all  ☐ Somewhat  ☐ Moderately  ☐ Quite a bit

5) Participating in social activities outside your home?

☐ Not at all  ☐ Somewhat  ☐ Moderately  ☐ Quite a bit

6) Emotional health (nervousness, depression, etc)?

☐ Not at all  ☐ Somewhat  ☐ Moderately  ☐ Quite a bit

7) Feeling frustrated?

☐ Not at all  ☐ Somewhat  ☐ Moderately  ☐ Quite a bit

Thank you for taking the time to complete this survey!